Pregnancy & Kidney Transplantation

Marleen van Buren

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Maria Cornelia van Buren

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Pregnancy and Kidney Transplantation

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Prof. dr. S.P. Berger
Dr. J.W. Ganzevoort

Copromotoren: Dr. J. van de Wetering
Dr. A.T. Lely

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Chapter 1

General Introduction

General Introduction

Kidney Transplantation and incidence of pregnancy

The incidence of end stage renal disease (ESRD) is increasing worldwide. ESRD is defined as an Glomerular Filtration Rate (GFR) below 15 ml/min/1.73m^2 [1]. ESRD can be treated with three sorts of renal replacement therapies: kidney transplantation (KT), peritoneal dialysis and hemodialysis [2]. KT is the best treatment option for most ESRD patients, because it improves survival and quality of life when compared to dialysis treatments [3]. Nevertheless, kidney transplant recipients (KT-recipients) have to be monitored closely, as immunosuppressive drugs are required to prevent graft rejection.[4] These immunosuppressive drugs increase the risk of infections, malignancies and cardiovascular disease [5-8].

In 2020, 18071 people received renal replacement therapy in the Netherlands[9]. Of this group, 1093 (6%) were women aged 44 years or younger[9]. The vast majority of these women (79%, 867/1093) was living with a kidney transplant [9]. ESRD can negatively affect hypothalamic-gonadal function and fertility [10]. One of the benefits of KT for these women is the recovery of fertility, as gonadal function can recover in just weeks after KT [11,12]. Since the first successful pregnancy after KT in 1958 [13], annual numbers of pregnancies after KT are rising. In the US, annually 227 KT-recipients conceive and give birth [14]. In 2018 The International Transplant Pregnancy Registry (ITPR) reported 1993 pregnancies in 1101 KT-recipients in the United States [15]. The exact number of women who have become pregnant after KT in the Netherlands is not known.

Pregnancy and the kidney: healthy women versus women with chronic kidney disease

During pregnancy the kidneys endure hemodynamic, renal tubular and endocrine changes. The kidney increases production of erythropoietin, active vitamin D and renin[16]. The adaptation of the (healthy) maternal body to pregnancy begins with hemodynamic and urinary tract alterations as early as 6 weeks after conception. The maternal systemic vascular resistance drops, causing a decrease in mean arterial pressure, which is at its lowest level between 8-24 weeks after conception [17,18]. Cardiac output increases as a result of the decrease in afterload. Increased effective renal plasma flow (ERPF) leads to an increase in glomerular filtration rate (GFR). This mid-term hyperfiltration, or gestational hyperfiltration, causes a relative decrease of serum creatinine and urea. The tubular response to circulating hormones is changed, as a fall in plasma albumin can be observed as well as a rise in serum cholesterol

[18]. The kidneys appear larger on ultrasound as dilatation of the calices, pyelum and ureters occurs [19] (**Figure 1**).

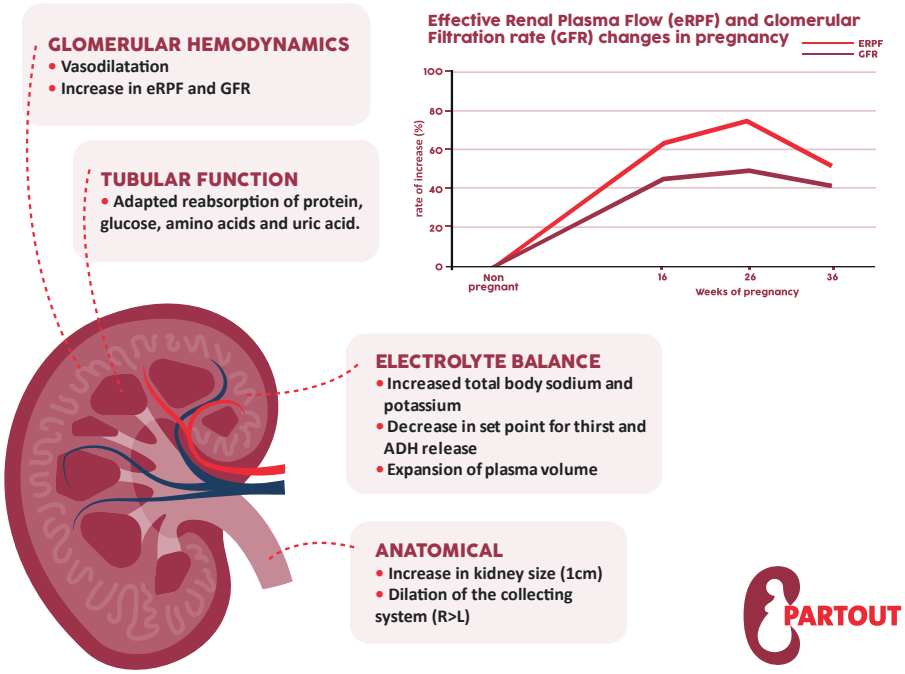

Figure 1: Normal pregnancy and the kidney

It has been shown that kidneys in women with Chronic Kidney Disease (CKD) are less able to make the before mentioned adaptions. Sick kidneys are less able to boost renal hormones such as erythropoetine and renine, this often leads to normochromic normocytic anaemia, reduced expansion of plasma volume, and vitamin D deficiency[20]. The gestational rise in GFR appears to be smaller in women with moderate kidney disease and absent in women with a serum creatinine higher than 200 µmol/l [21-23]. Women with CKD have an increased risk of poor pregnancy outcome and an accelerated decline in renal function [21,24-26]. although there have been studies published that did not observe this accelerated decline [27]. A pregnancy in women undergoing dialysis is associated with increased maternal and fetal risk [28,29].

Effect of pregnancy on the kidney transplant

After KT the transplanted kidney develops compensatory renal hypertrophy, which results in hyperfiltration [30 31]. The increased plasma flow during pregnancy in addition to the already existing hyperfiltration may cause progressive loss of graft func-

tion due to glomerular sclerosis [30]. Furthermore, it might be possible that there is increased pressure in the kidney during pregnancy, although this was not measured in historic micropuncture studies in pregnant rodent models [32]. It is unknown whether this temporary increase in glomerular pressure has an effect on death censored graft loss (DCGL). These insights would be of great importance to pre-conceptional counseling of KT-recipients.

Besides post-pregnancy DCGL, it is unknown what the effect of pregnancy is on the course of graft function in KT-recipients. Women with gestational hypertension show a decrease in estimated glomerular filtration rate (eGFR) instead of the normal physiological increase in during pregnancy [33]. However, in these women the temporary decrease in eGFR during pregnancy did not persist or progress after pregnancy [34]. The absence of midterm hyperfiltration is related to worse pregnancy outcomes in the general population [35]. Bramham et al described an absence of the physiologic fall in serum creatinine (SCr) levels during pregnancy, in almost 49% of KT-recipients. However, no relationship between the absence of a decrease in SCr and adverse pregnancy outcomes was found [36]. Whether the absence or presence of midterm hyperfiltration during pregnancy has an effect on long-term eGFR in KT-recipients is at present unknown.

Pre-pregnancy counseling of kidney transplant recipients

Although the first successful pregnancy after KT has been reported in 1958 [13] and many years have passed since then, nephrologists have been reluctant to give a positive pregnancy advice to KT-recipients. Only women who had an excellent graft function were granted 'permission' to become pregnant. KT-recipients that did not meet the criteria from the guidelines such as creatinine <1,5 mg/dl (133 µmol/L) and no or minimal proteinuria were negatively counseled [37,38].

KT-recipients have the same desire to conceive as women in the general population[39,40]. Despite the importance of the topic, there are only a few qualitative studies on perspectives on pregnancy among KT-recipients. To date, only one qualitative study performed in Australia has focused specifically on pregnancy among women with CKD [41]. Pregnancy in the context of CKD requires women to think about their own survival, disease status and possible guilt towards their family. Furthermore, limited research is available on the experiences of women raising children after KT [42].

Hence, pre-pregnancy counseling is an important aspect of clinical care for KT-recipients. According to the best practice guidelines dating from 2002 (European) and 2005 (USA) [37,38], the optimal timing of pregnancy after KT is one to two years after KT. The optimal conditions are described: a good renal function, little or no proteinuria, normal blood pressure, no acute recent rejection, good compliance

to antihypertensive and immune suppressive medication and no use of teratogenic drugs. Furthermore, it is advised to evaluate pregnancies outside these criteria on a case-by-case basis.

Although the ideal setting for pregnancy after KT has been described, data are lacking about pregnancy in less optimal situations. Furthermore, from previous studies it is known that physicians do not always follow clinical practice guidelines[43,44].

Pregnancy outcomes in kidney transplant recipients

Pregnancy in KT-recipients is associated with increased fetal and maternal risks for adverse pregnancy outcome. Therefore, these pregnancies are labelled as high risk. Reported live birth rates after KT are consistently between 72% and 80%[45-47]. Compared to the US general population, pregnancies after KT are associated with higher rates of preterm birth < 37 weeks of gestation (45,6% versus 12,5%), a higher incidence of babies born small for gestational age or with a low birth weight (mean birth weight 2420 versus 3298 gram) [45,47]. In addition, the pregnancies are reported to have high maternal complication rates, such as (worsening of) hypertension, proteinuria and an increased risk to develop (superimposed) pre-eclampsia (27% versus 3%) [48]. It has not been established whether the absence of a gestational rise in GFR or midterm hyperfiltration is also related with pregnancy outcomes and long-term term outcome in KT-recipients.

Most data on pregnancy outcomes after KT comes from the ITPR, which holds mainly US data [15]. In **Table 1** the results of the ITPR and results of three European cohorts are presented[36,46,49]. Live birth rate is similar between the different cohorts, ranging from 74% to 77%. Mean birthweight was higher in the Norwegian study which could be caused by a higher mean gestational age [49]. The differences between the studies and the ITPR registry can be caused by either different treatment protocols or health differences between populations, such as baseline serum creatinine values. Of note, it is important to realise that the ITPR is a voluntary registry. This might cause bias of outcomes when KT-recipients who have had adverse pregnancy outcomes were not included. Furthermore, socioeconomic factors may cause loss of follow-up. To add, previous studies on risk factors for adverse pregnancy outcomes are also limited to voluntary registries, a selected group of KT-recipients or no careful handling of missing data. Thus, there is a need for a larger and objective cohort of women with a pregnancy after KT to study pregnancy outcomes and risk factors for adverse pregnancy outcomes.

Table 1: Literature on pregnancy outcomes after Kidney Transplantation (KT)

	ITPR 2018 [15]	Norway 2016 [49]	Scotland 2016 [46]	United Kingdom 2013 [36]
KT recipients	1197	119	89	101
Pregnancies	2142	119	138	105
Live birth rate	75%	NR	74%	91%
Gestational age (weeks)*	35.8 (±NR)*	36.4 (±3)*	34.3 (24-37)**	36 (27-43)**
Prematurity < 37 weeks	48%	38%	61%	52%
Birth weight (grams)	2561 (±NR)*	2763 (±733)*	2464 (±727)*	NR
Low birth weight < 2500 gram	43%	31%	45%	48%
Gestational hypertension	48%	NR	8%	NR
Preeclampsia	30%	40%	14%	24%

ITPR: International Transplant Pregnancy Registry. NR: Not Reported, *Mean (standard deviation), **Median (range)

Living kidney donation and pregnancy

Kidney transplantation is the best treatment for ESRD, although not all kidney transplants are equal. Living donor allografts have better survival rates than deceased donor kidneys [50], providing better outcomes for the KT recipient. Little is known about the long-term effects of living kidney donation (LKD) on the health of the donor, especially for younger donors. Current literature shows reassuring results, without increment of cardiovascular risk for donors compared to the general population [51,52]. A substantial number of donors are women of reproductive age. Therefore, it is of great importance to know if LKD affects pregnancy outcomes and if pregnancy affects long-term function of the mono-kidney.

Previous research shows that after LKD the pre-donation GFR is reduced by approximately 30% [53]. The remaining kidney experiences compensatory hypertrophy, hyperfiltration and an increase in GFR. As described earlier, a similar increase in GFR is seen during pregnancy, when GFR and RPF increase by 40-65% and 50-85% respectively [54]. A pregnancy potentially adds an additional strain of hyperfiltration on the mono-kidney after LKD [55]. It is unknown what effect this additional hyperfiltration has on the long-term function of the mono-kidney.

In the general population, pregnancy with reduced GFR due to CKD is associated with adverse pregnancy outcomes [27]. Research is limited on pregnancy outcomes in otherwise healthy kidney donors. Retrospective cohorts show inconsistent results on pregnancy after LKD [56-60]. The majority of studies describe a higher risk of hypertensive disorders in pregnancy after LKD compared to the general population and pregnancies before LKD. An overview of the four studies from different countries is

given in **Table 2**. The differences in outcomes can be mainly explained by differences in definition of gestational hypertension and preeclampsia. Furthermore, the heterogeneity in these study groups makes it hard to identify if these risks are applicable to the Dutch population.

Table 2: Literature on pregnancy outcomes after Living Kidney Donation (LKD)

	Norway 2008 [56]	USA 2009 [60]	Canada 2015 [57]	South Korea 2018 [58]
LKD women	69	239	85	56
Pregnancies	106	490	131	56
Stillbirth	3%	<1%	NR	2%
Prematurity < 37 weeks	9%	9%	8%	0%
Birth weight (grams)	3065 (2750-3480)**	NR	NR	NR
Low birth weight < 2500 gram	8%	NR	6%	0%***
Gestational hypertension	3%	7%	6%	5%
Preeclampsia	6%	7%	6%	4%

Median (range), * < 2700 gram

Aims and scope of this thesis

As described earlier, data and outcomes of pregnancy after KT are not always representative of the Dutch population. For this reason the PARTOUT network (Pregnancy After Renal Transplantation OUTcomes) has been established; a network group connecting all seven university medical centers in the Netherlands. In this network, gynecologists, nephrologists, a nurse practitioner, an epidemiologist and an immunologist work together. The goal of this network is to collect data on pregnancies after KT and therefore have better insight in the current outcomes of the mother, child and the kidney graft in the Netherlands.

The overall aim of this thesis is to provide insight in outcomes of pregnancy for the mother, child and graft. Using these findings, pregnancy counseling can be improved for KT-recipients, transplant professionals and women who want to donate their kidney and have a future pregnancy wish.

- The first part of this thesis focuses on the effect of pregnancy on the transplanted kidney and the outcomes of pregnancy after KT in the Netherlands.
- The second part elaborates on aspects of counseling, experiences of KT-recipients and KT professionals.

- The third part describes the effect of pregnancy on the mono-kidney and the outcomes of pregnancies in women after LKD **(Figure 2).**

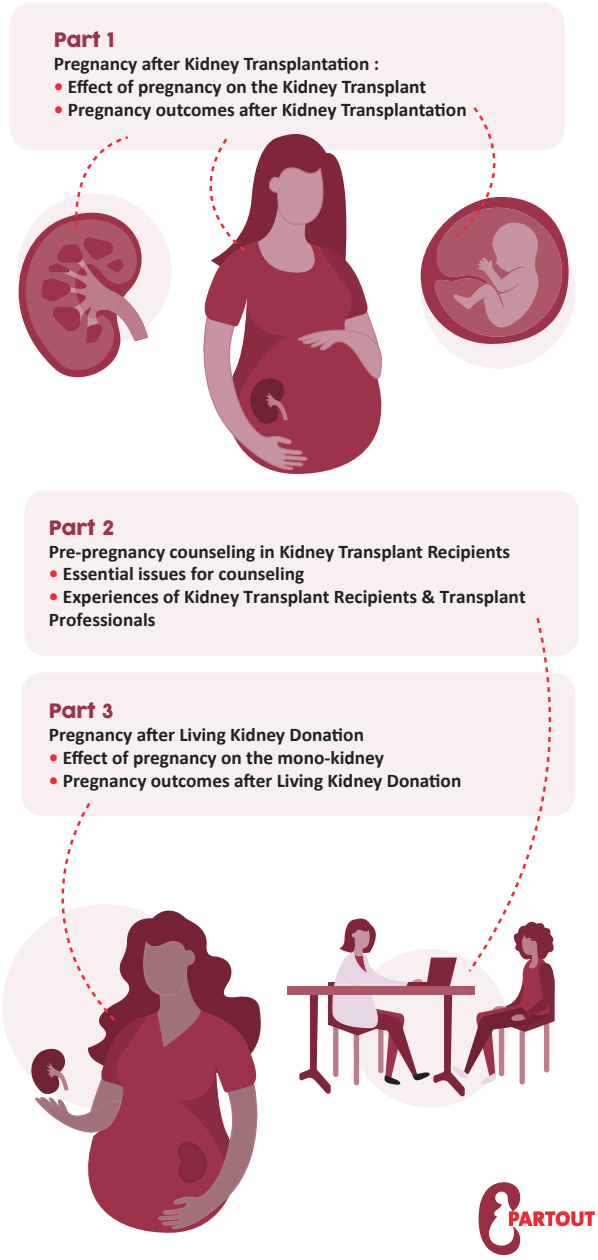

Figure 2: Content of this thesis

Part 1

Effect of pregnancy on the transplanted kidney and pregnancy outcomes after KT

- To perform an updated meta-analysis of graft survival with a comparison with non-pregnant KT-recipients and, for the first time, long-term (up to 10 y) graft function (SCr) after pregnancy. Second, to give an overview of predictors for adverse long-term graft outcomes after pregnancy by performing a systemic review of the literature **(Chapter 2).**
- To evaluate individual eGFR slopes before and after pregnancy in the Netherlands and identify the most important predictors for eGFR slope decline and DCGL following pregnancy after KT **(Chapter 3).**
- To analyze absolute risks of adverse pregnancy outcomes per pre-pregnancy eGFR-CKD-category in a consecutive, multicenter cohort of KT-recipients in the Netherlands including every pregnancy after KT in the past forty years nationwide. Second, to identify independent predictors of adverse pregnancy outcomes **(Chapter 4).**

Part 2

Essential issues for pre-pregnancy counseling in kidney transplant recipients

- To highlight the importance of including; long-term prognosis after pregnancy, the risk of graft failure, raising a child while being on dialysis, the risk of death in pre-pregnancy counseling. **(Chapter 5).**
- To identify the incidence of women getting pregnant after KT and explore motives pro-and against pregnancy, together with psychosocial and medical factors involved in decision making. Second, to explore experiences of pregnancy and child-raising **(Chapter 6).**
- To examine the variation in attitude of medical specialists regarding pregnancy after KT in less ideal situations. Second, to examine decision factors for this attitude **(Chapter 7).**

Part 3

The effect of pregnancy on the remnant mono-kidney in women after LKD and pregnancy outcomes after LKD

- To assess if long term kidney function after LKD is prone to a faster decline after pregnancy and secondly if pregnancies after LKD have a higher risk of complications than pregnancies before LKD **(Chapter 8).**

References

1. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med.* 2013;158(11): 825-830.
2. Gomez CG, Valido P, Celadilla O, Bernaldo de Quiros AG, Mojon M. Validity of a standard information protocol provided to end-stage renal disease patients and its effect on treatment selection. *Perit Dial Int.* 1999;19(5): 471-477.
3. Suthanthiran M, Strom TB. Renal transplantation. *N Engl J Med.* 1994;331(6): 365-376.
4. Kasiske BL ZM, Chapman JR, Craig JC, Ekberg H et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney International.* 2010;77: 299-311.
5. Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med.* 2004;351(26): 2715-2729.
6. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med.* 2007;357(25): 2601-2614.
7. Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. *JAMA.* 2006;296(23): 2823-2831.
8. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. *Transplantation.* 2006;82(5): 603-611.
9. Nefrovisie. Landelijke cijfers. <**https://ivisualz.nl/ivisualz/chartFlash/charts**> Published 2021. Accessed 01-12-2021 2021.
10. Leavey SF, Weitzel WF. Endocrine abnormalities in chronic renal failure. *Endocrinol Metab Clin North Am.* 2002;31(1): 107-119.
11. Davison JM. Dialysis, transplantation, and pregnancy. *Am J Kidney Dis.* 1991;17(2): 127-132.
12. McKay DB, Josephson, M. A. Pregnancy in Recipients of Solid Organs - Effects on Mother and Child. *The New Engeland Journal of Medicine.* 2006;354(12): 1281-1293.
13. Murray JE RD, Harrison JH, Merril JP. Successful Pregnancies after Human Renal Transplantation. *The New Engeland Journal of Medicine.* 1963;269: 341-343.
14. BE Hamilton JM, MJK Osterman, LM Rossen. Provisional Data for 2018 CDC. In: Statistics DoV, ed: National Center for Health Statistics.; 2018.
15. Moritz MJ CS, Coscia LA, et al. Transplant Pregnancy Registry International (TPR). *2017 annual report.* Philadelphia PA: Gift of Life Institute; 2018:0-21.
16. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ.* 2008;336(7637): 211-215.
17. Halligan A, O'Brien E, O'Malley K, et al. Twenty-four-hour ambulatory blood pressure measurement in a primigravid population. *J Hypertens.* 1993;11(8): 869-873.
18. Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int.* 1998;54(6): 2056-2063.
19. Faundes A, Bricola-Filho M, Pinto e Silva JL. Dilatation of the urinary tract during pregnancy: proposal of a curve of maximal caliceal diameter by gestational age. *Am J Obstet Gynecol.* 1998;178(5): 1082-1086.
20. Williams D. Renal Disorders. In: James DK SP, Weiner CP, Gonik B, ed. *High risk pregnancy. Management options.* 3rd ed. Philadelphia: Elsevier Saunders; 2006:1098-1124.

21. Jungers P, Chauveau D, Choukroun G, et al. Pregnancy in women with impaired renal function. *Clin Nephrol.* 1997;47(5): 281-288.
22. Jungers P, Houillier P, Chauveau D, et al. Pregnancy in women with reflux nephropathy. *Kidney Int.* 1996;50(2): 593-599.
23. Cunningham FG, Cox SM, Harstad TW, Mason RA, Pritchard JA. Chronic renal disease and pregnancy outcome. *Am J Obstet Gynecol.* 1990;163(2): 453-459.
24. Fischer MJ, Lehnerz SD, Hebert JR, Parikh CR. Kidney disease is an independent risk factor for adverse fetal and maternal outcomes in pregnancy. *Am J Kidney Dis.* 2004;43(3): 415-423.
25. Imbasciati E, Gregorini G, Cabiddu G, et al. Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. *Am J Kidney Dis.* 2007;49(6): 753-762.
26. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. *N Engl J Med.* 1996;335(4): 226-232.
27. Piccoli GB, Cabiddu G, Attini R, et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. *J Am Soc Nephrol.* 2015;26(8): 2011-2022.
28. Piccoli GB, Minelli F, Versino E, et al. Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes. *Nephrol Dial Transplant.* 2016;31(11): 1915-1934.
29. Hladunewich MA, Hou S, Odutayo A, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. *J Am Soc Nephrol.* 2014;25(5): 1103-1109.
30. Davison JM. The effect of pregnancy on kidney function in renal allograft recipients. *Kidney Int.* 1985;27(1): 74-79.
31. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. *Br J Obstet Gynaecol.* 1981;88(1): 1-9.
32. Baylis C. The mechanism of the increase in glomerular filtration rate in the twelve-day pregnant rat. *J Physiol.* 1980;305: 405-414.
33. Lopes van Balen VA, van Gansewinkel TAG, de Haas S, et al. Maternal kidney function during pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2019;54(3): 297-307.
34. Paauw ND, van der Graaf AM, Bozoglan R, et al. Kidney Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study. *Am J Kidney Dis.* 2018;71(5): 619-626.
35. Park S, Lee SM, Park JS, et al. Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of Gestational Hyperfiltration. *Clin J Am Soc Nephrol.* 2017;12(7): 1048-1056.
36. Bramham K, Nelson-Piercy C, Gao H, et al. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol.* 2013;8(2): 290-298.
37. McKay DB, Josephson MA. Reproduction and Transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. *American Journal of Transplantation.* 2005;5(7): 1592-1599.
38. Transplantation EEGoR. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant.* 2002;17 Suppl 4: 50-55.
39. Szpotanska-Sikorska M, Mazanowska N, Madej A, Kociszewska-Najman B, Wielgos M, Pietrzak B. Reproductive life planning in women after kidney or liver transplantation. *Clin Transplant.* 2018;32(9): e13378.

40. Crowley-Matoka M. Desperately seeking "normal": the promise and perils of living with kidney transplantation. *Soc Sci Med.* 2005;61(4): 821-831.
41. Tong A, Brown MA, Winkelmayer WC, Craig JC, Jesudason S. Perspectives on Pregnancy in Women With CKD: A Semistructured Interview Study. *Am J Kidney Dis.* 2015;66(6): 951-961.
42. Yoshikawa Y, Uchida J, Kosoku A, Akazawa C, Suganuma N. Childbirth and Care Difficulties of Female Kidney Transplantation Recipients. *Transplant Proc.* 2019;51(5): 1415-1419.
43. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA.* 1999;282(15): 1458-1465.
44. Vendittelli F, Riviere O, Crenn-Hebert C, Giraud-Roufast A, Audipog Sentinel N. Do perinatal guidelines have an impact on obstetric practices? *Rev Epidemiol Sante Publique.* 2012;60(5): 355-362.
45. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant.* 2011;11(11): 2388-2404.
46. Stoumpos S, McNeill SH, Gorrie M, et al. Obstetric and long-term kidney outcomes in renal transplant recipients: a 40-yr single-center study. *Clin Transplant.* 2016;30(6): 673-681.
47. Sibanda N BJ, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: A report from the UK transplant registry. *Transplantation.* 2007;83(10): 1301-1307.
48. Chittka D, Hutchinson JA. Pregnancy After Renal Transplantation. *Transplantation.* 2017;101(4): 675-678.
49. Majak GB, Sandven I, Lorentzen B, et al. Pregnancy outcomes following maternal kidney transplantation: a national cohort study. *Acta Obstet Gynecol Scand.* 2016;95(10): 1153-1161.
50. Port FK, Dykstra DM, Merion RM, Wolfe RA. Trends and results for organ donation and transplantation in the United States, 2004. *Am J Transplant.* 2005;5(4 Pt 2): 843-849.
51. O'Keeffe LM, Ramond A, Oliver-Williams C, et al. Mid- and Long-Term Health Risks in Living Kidney Donors: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2018;168(4): 276-284.
52. Janki S, Dehghan A, van de Wetering J, et al. Long-term prognosis after kidney donation: a propensity score matched comparison of living donors and non-donors from two population cohorts. *Eur J Epidemiol.* 2020;35(7): 699-707.
53. Blantz RC, Steiner RW. Benign hyperfiltration after living kidney donation. *J Clin Invest.* 2015;125(3): 972-974.
54. Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy. *Kidney Int.* 1980;18(2): 152-161.
55. Odutayo A, Hladunewich M. Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. *Clin J Am Soc Nephrol.* 2012;7(12): 2073-2080.
56. Reisæter AV, Røislien J, Henriksen T, Irgens LM, Hartmann A. Pregnancy and Birth After Kidney Donation: The Norwegian Experience. *American Journal of Transplantation.* 2009;9(4): 820-824.
57. Garg AX, Nevis IF, McArthur E, et al. Gestational hypertension and preeclampsia in living kidney donors. *N Engl J Med.* 2015;372(2): 124-133.
58. Yoo KD, Lee H, Kim Y, et al. Maternal and fetal outcomes of pregnancies in kidney donors: A 30-year comparative analysis of matched non-donors in a single center. *Kidney Res Clin Pract.* 2018;37(4): 356-365.
59. Davis S, Dylewski J, Shah PB, et al. Risk of adverse maternal and fetal outcomes during pregnancy in living kidney donors: A matched cohort study. *Clin Transplant.* 2019;33(1): e13453.
60. Ibrahim HN, Akkina SK, Leister E, et al. Pregnancy outcomes after kidney donation. *American Journal of Transplantation.* 2009;9(4): 825-834.

PART 1

Pregnancy after Kidney Transplantation

Chapter 2

Long term graft survival and graft function following pregnancy in kidney transplant recipients: a systematic review and meta-analysis

Marleen C. van Buren, Anouk Schellekens*,*
T. Katrien J. Groenhof, Franka van Reekum,
Jacqueline van de Wetering, Nina D. Paauw, A. Titia Lely
**Authors contributed equally*

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ABSTRACT

Background

The incidence of pregnancy in kidney transplant (KT) recipients is increasing. Studies report that the incidence of graft loss (GL) during pregnancy is low, but less data is available on long-term effects of pregnancy on the graft.

Methods

Therefore, we performed a meta-analysis and systematic review on GL and graft function, measured by serum creatinine (SCr), after pregnancy in KT recipients, stratified in years post-partum. Furthermore, we included studies of nulliparous KT recipients

Results

Our search yielded 38 studies on GL and 18 studies on SCr. The pooled incidence of GL was 9.4 % within two years post-pregnancy, 9.2% within two to five years, 22.3% within five to ten years and 38,5% more than ten years post-partum. In addition, our data show that, in case of graft survival, SCr remains stable over the years. Only within 2 years postpartum Δ SCr was marginally higher (0.18 mg/dL, 95%CI [0.05-0.32], p = 0.01). Furthermore, no differences in GL was observed in ten studies comparing GL post-pregnancy with nulliparous controls. Systematic review of the literature showed that mainly pre-pregnancy proteinuria, hypertension and high SCr are risk factors for GL.

Conclusions

Overall, these data show that pregnancy after KT has no effect on long-term graft survival and only a possible effect on graft function within 2 years postpartum. This might be due to publication bias. No significant differences were observed between pre and postpartum SCr at longer follow-up intervals.

INTRODUCTION

With increasing numbers of kidney transplantation (KT) performed worldwide and good short-term pregnancy as well as graft outcomes, there is an increasing incidence of pregnancy in KT patients. In 2011 over 11.000 births after KT have been reported worldwide [1]. The Transplant Pregnancy Registry International (TPR) reported in 2018, 1993 pregnancies in 1101 KT recipients in the United States [2]. Pregnancy in KT recipients is labeled as high risk with increased fetal and maternal risks for adverse pregnancy outcome. Reported live birth rates after KT are consistently between 72% and 80% [1,3,4]. Compared to the US general population, pregnancies after KT are associated with higher rates of cesarean sections (56,9% versus 31,9%), preterm (< 37 weeks of gestation) deliveries (45,6% versus 12,5%) and increased rates of small for gestational age and low birth weight (mean birth weight 2420 versus 3298 grams) [1,4]. In addition, the pregnancies are reported to have high maternal complication rates of hypertension and proteinuria [5]: with an increased risk to develop pre-eclampsia 27% versus 3%. In previous meta-analysis 4,2% of recipients experienced an episode of acute rejection during their pregnancy [1].

Besides the pregnancy related complications mentioned above, little is known on what effect pregnancy has on long-term graft survival and graft function. At the time of KT the transplanted kidney develops compensatory renal hypertrophy, which results in hyperfiltration [6]. During pregnancy, physiological changes occur in the kidney and cardiovascular system, including vasodilatation and increase in glomerular filtration rate (GFR) [7]. This increased pressure and/or plasma flow during pregnancy on top of the already existing hyperfiltration may cause progressive loss of graft function due to glomerular sclerosis [6]. It is unknown which effect this temporary extra demand has on the long-term graft survival and graft function. These insights would be helpful in pre-conceptional counseling of KT patients.

A meta-analysis KT recipients published in 2011 analysed GL incidence in a small number of retrospective studies, reporting 8% post pregnancy GL at 2 years, 7% at 5 years and 19% at 10 years [1]. Limited studies reviewed a year later showed no significant increase in SCr at 3 months and GL at 2 years postpartum [8]. No reviews analyzed the effect on long-term consequence of pregnancy on graft function (SCr).

A limitation of previous meta-analysis and reviews is that they did not include a control group of nulliparous KT recipients [1,8]. Furthermore, they do not systematically report on predictive factors regarding long-term graft function after pregnancy.

Currently, optimal timing of pregnancy after KT are described as: an interval of > 1 year between KT and pregnancy, and an interval of >1 year between the last episode of acute rejection. Furthermore, serum creatinine (SCr) levels should be

below 1,5 mg/dl, no acute infections should be present and stable maintenance of non-teratogenic immunosuppressive medication [9,10]. However, the aforementioned guidelines are based mainly on data from voluntary registries and expert opinions, focusing primarily on (predictors of) adverse pregnancy outcomes.
To increase insight in the effect of pregnancy on long-term graft survival and function as guidance for preconceptional counseling: the aim of this study was to perform an updated meta-analysis on graft survival with comparison with non-pregnant KT recipients and for the first time long-term (up to ten year) graft function (SCr) after pregnancy. We included new studies since 2010 and studies with nulliparous KT recipient control groups. In addition, systematic review was performed to give an overview of predictors for adverse long-term graft outcomes after pregnancy.

METHODS

Search strategy and study selection

A systematic search of literature was performed in Pubmed, Embase and Cochrane library on to identify all studies on SCr and GL after pregnancy in KT recipients up till September 2018 (Appendix 1). Two reviewers (AS and NP) independently screened the abstracts of all eligible studies. Studies reported in English, focusing on SCr or GL following pregnancy in KT recipients were eligible. Furthermore, we conducted snowballing strategy to include eligible reports. Case studies, reviews and studies, which reported less than six months post-pregnancy follow-up were excluded.

Data extraction

Two independent reviewers (AS and MB) extracted data from all eligible studies. The following data were extracted from each study: study outcomes on pre-pregnancy SCr, post-pregnancy SCr and GL or graft survival. For all the included studies data on pre- and post-pregnancy SCr was extracted or calculated in mean ± SD (in mg/dL). When median with range were reported, the mean ± SD were calculated by the method of Hozo et al. [11]. SCr levels that were reported in µmol/L were converted into mg/dL. If graft survival was reported, this was converted to GL. In eleven studies there were missing or incomplete data, this was requested from the authors and in three cases we gained enough information to include them in our meta-analysis. Using the observational cohort studies with a control group, it was examined whether pregnancy affects GL or SCr, versus nulliparous KT recipients. In addition, all included studies were reviewed for different predictors of adverse graft outcomes (e.g. hypertension, proteinuria, SCr prior to pregnancy, transplant to conception interval).

Pooled estimates

In order to pool data on GL and post-pregnancy SCr, subcategories were created based on the number of years postpartum. Articles on GL were divided into four categories based on timing since pregnancy: GL within two year post-pregnancy, two to five year, five to ten year post-pregnancy, and more than ten year post-pregnancy. Data on SCr post-pregnancy was divided into three subcategories: within two year post-pregnancy, two to five years, and five to ten years post-pregnancy. The difference between post-pregnancy SCr and pre-pregnancy SCr (Δ SCr) was calculated. For binary outcomes (GL), pooled estimates and 95% confidence intervals were calculated using Excel [12]. For continuous outcomes (pre- and post-pregnancy SCr) pooled estimates and 95% confidence intervals were calculated using mean difference and random effect size, conducted by Review Manager 5.3.[13].

Quality assessment and assessment of publication bias

Two reviewers (AS and MB) screened the studies for full text and performed a critical appraisal on applicability and validity (Appendix 2). Every study was scored for design, size, domain, determinant, outcome, missing data, lost to follow up, standardization of outcome, analysis, confounding factors and the possibility to extract data. To test for publication bias we performed funnel plot analysis for every subtopic within GL and SCr.

RESULTS

As a result of the search from three electronic databases, 1416 studies qualified for abstract screening. Among these, 43 individual publications were selected for inclusion of which 38 studies reported on GL and 18 articles on SCr post-pregnancy (**Figure 1**). One study by Levidiotis [14] divided graft survival in different periods of time that is why we could only use the data of the sub analysis of the matched cohort. Ten of these were observational cohort studies with a control group [3,14-22], **Table 1** presents the study characteristics and reported graft outcomes for all of the included studies.

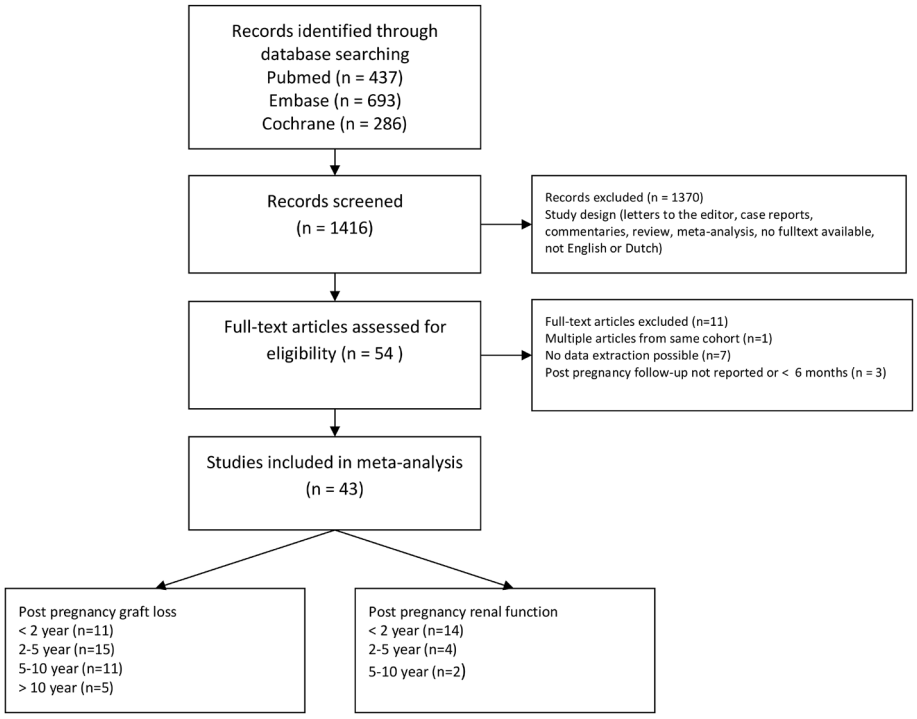

Figure 1: Study selection for studies reporting post-pregnancy graft function and/or post- pregnancy graft loss

Pooled incidence of graft loss after pregnancy in KT recipients

A total of 38 studies reported on graft loss in 2453 recipients. Median follow-up time was very heterogenic amongst the studies and varied from 6 months until 15 years after pregnancy GL occurred in 321 (13%) patients following pregnancy. The risk on GL is increasing in time with pooled incidences of respectively 9.4%, 9.2%, 22.3%, and 38.5% for less than two year, two to five year, five to ten year and more than ten year post-pregnancy (**Figure 2**A-D).

Among the ten studies with a nulliparous control groups, matching criteria differed as shown in **Table 2**. The median follow-up time of these studies was 100 months (range 45 - 168) post pregnancy.

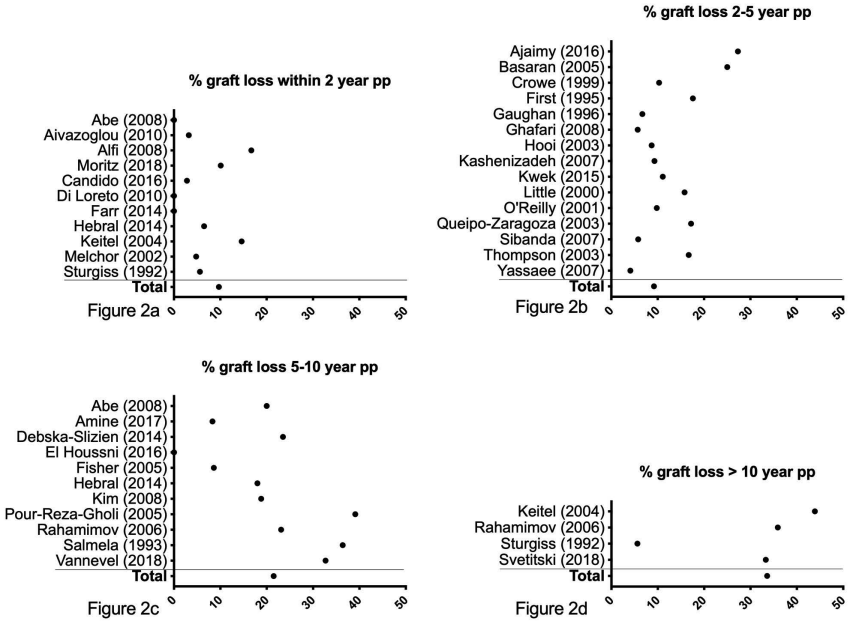

Figure 2A-D: Pooled incidence of post-pregnancy graft loss

2A. Graft loss within two year post-pregnancy: 9.4%, n=1347 (range 10-1100), total graft loss n=126 (range 0-111).

2B. Graft loss two to five years post-pregnancy: 9.2%, n=600 (range 8-139), total graft loss n=55 (range 1-8).

2C. Graft loss five to ten years post-pregnancy: 22.3%, n=395 (range 12-81), total graft loss n=88 (range 0-18).

2D. Graft loss more than ten year post-pregnancy: 38.5%, 234 (range 18-118), total graft loss n=90 (range 1-51).

Table 1: Study characteristics and outcomes

	Study years (country)	KT recipients (n)	Pregnancies*** (n)	Mean age at conception (years)
Abe (2008) [34]	1977-2002 Japan	20	21	32.1 (range 25-40) at delivery
Aivazoglou (2010) [31]	2006-2010 Brazil	31	34	26.5 (range 17-43)
Ajaimy et al (2016) [35]	2009-2014 USA	11	11	36 (range 22-38)
Alfi (2008) [32]	1989-2005 Saudi-Arabia	12	20	30.5 ± 4.5
Amine (2017) [47]	1992-2011 Tunisia	12	17	34.2
Areia (2009) [48]	1989-2007 Portugal	28	34	27 ± 5.1
Basaran (2004) [49]	1975-2003 Turkey	8	8	29.3 ± 4.7
Candido (2016)[41]	2004-2014 Portugal	36	41	28 ± 5
Crowe (1999) [30]	1972-1998 UK	29	33	29 (range 19-39)
Debska-Slizien (2014) [50]	1980-2012 Poland	17	19	30 ± 5
Di Loreto (2010) [51]	1997-2010 Italy	12	13	33.9 ± 3.1
El Houssni (2016) [52]	1998-2012 Morocco	12	18	29.9 ± 5.3
Farr (2014) [53]	1999-2013 Austria	10	12	34 ± 4
First (1995) [15]	1967-1990 USA	18	22	NR
Fischer (2005) [16]	NR Germany	81	81	29 ± 0.5 at delivery
Galdo (2005) [54]	1982-2002 Chile	30	29	NR
Gaughan (1996) [33]	1991-1996 USA	15	13	29.5 ± 5.2
Ghafari (2008) [36]	1991-2007 Iran	53	61	24.5 (range 19-38)
Gorgulu (2010) [55]	1983-2008 Turkey	19	19	29 ± 3
Hebral (2014) [56]	1969-2011 France	46	61	31 (24-43)
Hooi et al (2003) [27]	1975-2001 Malaysia	46	51	30.7 ± 4.7
Kashanizadeh (2007) [17]	1996-2002 Iran	86	62	NR
Kato (2012) [24]	1973-2009 Japan	23	22	31.3 ± 3.6 at delivery

Pre-pregnancy SCr (mg/dL)	Post-pregnancy SCr (mg/dL)	Graft loss (%)	Post pregnancy follow up (in months) ^	TCI (in months)
1.15 ± 0.27	1.29 ± 0.51	1 yr: 0% 5-10 yr: 20%	95	66 (range 24 – 135) *
NR	NR	3.2%	12	44.8 (range 4-120) n=19 without graft dysfunction 42.6 (range 6-104) n= 15 with graft dysfunction
NR	NR	27.3%	27.3 (range 14.4-48)	42.4
1.24 ± 0.27	1.76 ± 2.15	16.7%	NR	21 ± 5.7
NR	NR	10%	72	46.9
1.29 ± 0.34	1.34 ± 0.95	NR	12	51.3 ± 34.2 (3 – 134)
1.15 ± 0.2	1.42 ± 0.8	25%	67.2 ± 28.8 ‡	43.2 (range 22.8 – 51.6)
1.19 ± 0.07	1.59 ± 0.20	0.4%	SCr 12	51.3 ± 36
1.77 ± 1.18	1.91 ± 1.18	10.3%	SCr 12	43 ± 6.9 ** (5 – 121)
NR	NR	23.5%	102 (range 12-300)	40.8 ± 30
NR	NR	0%	24	53.4 ± 37.8 *
NR	NR	0%	112 (27.25)§	42 (47.5)§
NR	NR	0%	128 ± 50 ‡	79 ± 36 *
NR	NR	16.7%	82.8 (range 43.2 – 164.4)	59 (range 2 – 221)
NR	NR	8.6%	91.3 ± 5	41.8 ± 3.2
1.19 ± 0.38	1.38 ± 0.53	NR	12	46.6 ± 35.5 (6 – 108)
NR	NR	6.7%	24	70.8 ± 10.8
NR	NR	5.7%	32 (range 12-120)	32.4 (range 20.4 – 63.6)
1.06 ± 0.3	1.15 ± 0.29	NR	96 ± 36	60 ± 36
	NR	1 yr: 6.5% 5-10 yr: 18.3%	72	60 (222) §
1.27 ± 0.37	1.35 ± 0.44	8.7%	58.8 ± 42	54 ± 37.2
	NR	9.3%	45 ± 22	31 ± 15 (12 – 85)
1.16 ± 0.39	1.4 ± 0.8	8.7%	SCr 12	70.8 ± 38.2

Table 1: Study characteristics and outcomes *Continued*

	Study years (country)	KT recipients (n)	Pregnancies*** (n)	Mean age at conception (years)
Keitel (2004) [29]	1977-2001 Brazil	41	28	NR
Kim (2008) [18]	1991-2005 Korea	48	52	31.6 ± 4.1
Kwek (2015) [42]	2001-2012 Singapore	9	10	34.6 range 32.8-36.8) at delivery
Levidiotis (2009)[14]	1966-2006 Australia	118	118	NR for this sub analysis
Little (2000) [57]**Journ**	1985-1998 Ireland	19	25	30,3 (range 19.9-42.8)
Melchor (2002) [58]	1973-1998 Mexico	21	26	30.8 ± 7.1
Moritz (2018)[2]	1967-2017 USA	1100	1980	NR
O'Reilly (2001) [28]	1967-1998 UK	41	57	29.7 (range 18-37)
Pour-Reza-Gholi (2005) [19]	1984-2004 Iran	60	41	29.8 ± 4.7
Queipo-Zaragoza (2003) [23]	1980-2000 Spain	29	32	29.6 ± 4.8
Rahamimov (2006) [20]	1983-1998 Israel	39	55	NR
Salmela (1993) [59]	1964-1989 Finland	22	22	NR
Sibanda (2007) [4]	1994-2001 UK	176	157	30 (range 20-43) at delivery
Stoumpos (2016) [3]	1973-2013 UK	89	104	30.3 ± 5.1
Sturgiss (1995) [21]	1967-1987 UK	18	18	NR
Svetitsky (2018) [22]	2001- 2017 Israël	18	22	29.6 (range 23-39.2) at delivery
Thompson (2003) [25]	1976-2001 UK	24	42	30 (range 19-39)
Vannevel (2018) [38]	1988- 2015 Belgium, Canada Switzerland, Canada, Ireland & Austria	52	52	32.8 ± 4.5
Yassaee (2007) [60]	1996-2001 Iran	74	74	29.3 ± 6.7
Yildirim (2005) [61]	1998 – 2005 Turkey	17	16	27.6 ± 5.8

Serum creatinine (SCr) in mg/dL (in mean ± SD or median (range), ***: only pregnancies >24 weeks, follow up in months ^: in case of no mean follow up post-pregnancy was reported, an explanation of outcomes is reported, ‡: post-transplantation follow up, TCI: transplant to conception interval in months (mean ± SD, or mean (range), *TDI: transplant to delivery interval in months, ** SEM, §: median (IQR), NR: not reported.

Pre-pregnancy SCr (mg/dL)	Post-pregnancy SCr (mg/dL)	Graft loss (%)	Post pregnancy follow up (in months) ^	TCI (in months)
1.2 ± 0.5	2.0 ± 1.8	< 2 yr: 14.6% >10 yr: 43.9%	GL 24 SCr 6	NR
1.12 ± 0.25	1.1 ± 0.98	18.8%	114 (range 44.4 – 184.8) ‡	40.2 ± 27.1
1.39 ± 0.25	2.23 ± 1.26	11.1%	GL 37 SCr 12	69 (38 – 97) §
NR	NR	15 yr: 43.5	67.2	NR
1.59 ± 0.46	1.71 ± 0.68	15.8%	33.2 (range 1-115)	48 (range 2.4 – 102)
	NR	4.8%	24	49
NR	NR	< 2 yr: 10.1%	188.4 ± 132	5.4 ± 4.3
	NR	9.8%	60	92.4 (12 – 288)
	NR	39.1%	100.8 ± 48.5	27.5 (range 1– 114) §
	NR	17.2%	60	45.6 ± 40.7
	NR	5-10 yr: 23.1% >10 yr: 35.9%	168 (range 72-264) ‡	42 ± 27.1
	NR	36.4%	90	57.6 *
	NR	5.8%	24	72 (range 3 – 228)
1.45 ± 0.87	1 yr: 1.62 ± 1.21 5 yr: 1.86 ± 1.6 10 yr:1.51 ± 0.56	15.7%	98.4 (157.2) §	NR
1.06 ± 0.29	1.26 ± 0.83	>10 yr: 5.6%	144 (range 48 - 276)	132 ± 60
1.17 (range 0.7-3.1)			148.8 ± 57.4	75.7 (range 34-147.8)
1.18 ± 0.43	1.24 ± 0.69	16.7%	46 (range 12 - 151.2)	54 ± 37.2
NR	NR	33%	69.6 (range 15.6 – 330)	74 ± 45
NR	NR	4.1%	2	41 ± 9.5
1.18 ± 0.16	1.19 ± 0.12	0%	6	31.2 (range 3 – 98)

Tabel 2: Characteristics matched cohort studies on graft loss

	N		Reference point	Matched for	Median FU time after pregnancy (months)	Graft Loss (%)		Odds ratio	P
	Index	Control				Index	Control		
First (1995) USA	18	26 f 23 m	TCI	1, 2, 4, 6, 7	82.8 (range 43.2 – 164.4)	16.7	15.4 8.7	1.11 2.11	NS
Sturgiss (1995) UK	18	18	NR	5, 6	144 (range 48 - 276)	5.6	11.1	0.48	NS
Fischer (2005) Germany	81	81	TDI	1 - 4, 9, 13	91.3 ± 5	8.6	4.9	1.23	NS
Pour-Reza Gholi (2005) Iran	60	60	NR	1, 2, 9	100.8 ± 48.5	30.0	28.3	1.08	NS
Rahamimov (2006) Israël	39	117	TCI	1, 2, 6-12	168 (range 72 - 264)	NR	NR		NS
Kashanizadeh (2007) Iran	86	125	NR	1, 6, 7, 9, 11	45 ± 22	9.3	7.2	1.32	NS
Kim (2008) Korea	48	187	NR	1, 2, 9	114 (range 44.4 – 184.8)	18.8	21.4	0.85	NS
Leviodiotis (2009) Australia	118	118	NR	1, 2, 4, 5	67.2	43.5	44.3		NS
Stoumpos (2016) UK	89	83	TCI	1, 4, 5	98.4 (157.2) §	15.7	NR		NS
Svetitsky (2018) Israel	18	18	TDI	1, 2, 4, 6, 7,12,14	Index 148.8 (range 66-237.6) Control 152.4 (range 58.8-228)	27.3	13.6	2.50	NS

§ IQR, N number of participants, FU follow-up, KT kidney transplantation, ESRD (End-Stage-Renal-Disease), IS medicine Immunosuppressive Medicine, HLA MM (Human Leucocyte Antigen Mismatch), PRA (Panel Reactive Antibody), NR (not reported), TDI Transplant to delivery interval, TCI Transplant to conception interval. 1. Age at KT, 2. Year of KT, 3. KT center, 4. Pre-conc. Serum Creatinine, 5. Serum Creatinine, 6. Cause of End Stage Renal Disease, 7. Source of KT, 8. Ethnicity, 9. Immunosuppressive medication, 10. Donor Age, 11. HLA Mismatch/Panel reactive antibody%, 12. Number of KT, 13. Diabetes Mellitus, 14. Pre-conc. Proteinuria

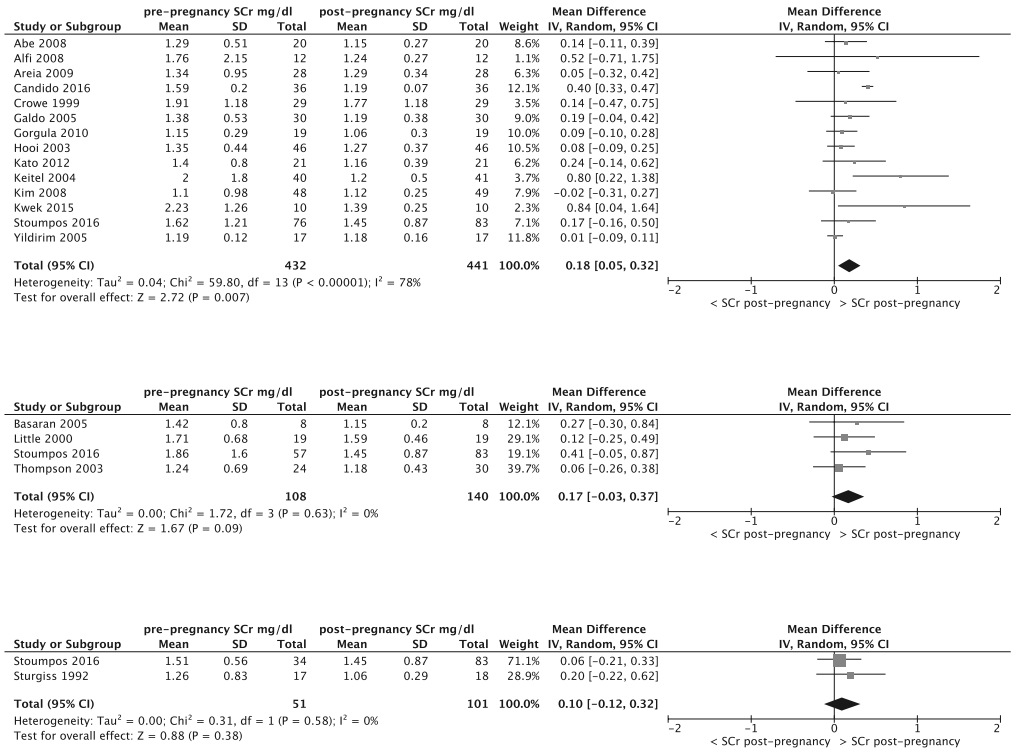

Figure 3A-C. Pooled difference (mean difference [95% CI] in pre-pregnancy SCr and post-pregnancy SCR (delta SCr pre- and post-pregnancy).

3A. Delta SCr within two year post pregnancy: SCr 0.18 mg/dL [0.05, 0.32], p=0.007, n=441

3B. Delta SCr two to five year post pregnancy: SCr 0.17 mg/dL [-0.03, 0.37], p=0.09, n=175

3C. Delta SCr five to ten year post pregnancy: SCr 0.10 mg/dL [-0.12, 0.32], p=0.38, n=101

Pooled incidence of SCr after pregnancy in KT recipients

The post-pregnancy data of 18 individual studies on SCr within women were pooled in three postpartum time intervals. Fourteen studies reported on one year post-pregnancy SCr in KT recipients. A pooled increase in SCr is seen of 0.18 mg/dL, 95% CI [0.05-0.32], p = 0.01 in the group comparing pre-pregnancy SCr with~~in~~ two year post-pregnancy SCr. (**Figure 3**A) Four studies reported on SCr two to five year following pregnancy, and only two studies on long term (five to ten year) post-pregnancy SCr and no significant differences were found when comparing pre- versus post-pregnancy SCr (**Figure 3**B-C).

Predictors of adverse outcomes on graft function and risk of graft loss

Among the included studies [3,4,16,18,19,22-33], different predictors of adverse outcomes on graft function were described, including hypertension prior to pregnancy, presence of proteinuria prior to pregnancy, preeclampsia, SCr prior to pregnancy, and transplant to conception interval (TCI). An overview of the literature on these risk factors is given and described in more detail below (**Table 3**). In addition to these most reported risk factors some incidental risk factors were reported. Type of delivery or type of donor was no significant risk factor for GL [34]. High panel reactive antibody (PRA) levels and donor specific anti-HLA antibodies (DSA) have a high risk of antibody mediated rejection (AMR) and have more pre-eclampsia [35]. The type of immunosuppressive regime had no effect on graft survival [23,36].

Pre-conceptional hypertension as a risk factor for accelerated graft loss

Four studies reported an effect of hypertension, before, or at the beginning of pregnancy, in relation to long-term graft function [4,23,24,34]. Hypertension was defined as bloodpressure >140/90 mmHg. These four authors concluded that (drug treated) hypertension prior to pregnancy is associated with worse graft function or is a risk factor for graft function decline and, or chronic rejection. In one of these studies post-pregnancy graft function (SCr) was compared between patients with hypertension prior to pregnancy (n = 5), and no hypertension prior to pregnancy (n = 15). The SCr was significantly worse (p = 0.03) in patients with hypertension prior to pregnancy [34]. Another study showed that hypertensive patients (n = 28) compared to normotensive patients (n = 23) had worse graft function (SCr) prior to pregnancy (1.39 mg/dL vs 1.10 mg/dL) p = <0.01) [28]. Two recent studies of which one was a matched cohort study did not see a relation between graft failure and chronic hypertension [22].

Table 3 Predictors of graft loss or renal function deterioration after pregnancy

Risk factors	Negative association		No association	
	Unit	*Author*	*Unit*	*Author*
Hypertension Before or at the beginning of pregnancy	>140/90 mmHg Drug treated hypertension	Queipo Zaragoza (2003) Sibanda (2007), Abe (2008), Kato (2012)	Pre-existing hypertension Chronic hypertension Chronic hypertension	Stoumpos (2016) Svetitsky (2018) Vannevel (2018)
Proteinuria	> 1 gram/day	Queipo Zaragoza (2003)	> 0.3 gram/day > 0.5 gram/day	Thompson (2003) Rocha (2013)
Pre-eclampsia	Borderline effect (OR, 1.09; 95% CI [0.92-1.34] P =0.09).	Svetitsky (2018)	-2.69 (-14.54 to 9.15) *P* = 0.65	Vannevel (2018)
Pre-pregnancy SCr	> 1.47 – 1.50 mg/dl > 1.69 – 1.75 mg/dl > 2.10 mg/dl Worse graft function (OR 1.71; 95% CI [CI 1.15-3.45] *P* = 0.04)	O'Reilly (2001), Alfi (2008) Thompson (2003), Keitel (2004) Kim (2008), Crowe (1999), Queipo Zaragoza (2003) Aivazoglou (2010) Svetitsky (2018)	< 2.26 mg/dl < 1.3 mg/dl Worse graft function (OR - 0.11 95% CI [-0.44 to 0.23] *P* = 0.52)	Hooi (2003) Rocha (2013) Vannevel (2018)
Age at transplantation	Older age (OR 1.13; 95% CI [1.03-1.21] *P* = 0.03)	Svetitsky (2018)		
Transplant to conception interval	< 1 year	Alfi et al. (2008)	General < 1 year < 2 year > 5 year Months (OR 0.05 95% CI [-0.07 to 0.18] *P* = 0.42)	Stoumpos (2016) Pour-Reza-Gholi (2005) Fischer (2005) Gaughan (1996) Vannevel (2018)

SCr: serum creatinine

Pre-conceptional proteinuria and pre-conceptional SCr as risk factors for accelerated graft loss

Proteinuria prior to or during pregnancy, especially proteinuria of more than 1g/day, is associated with worse graft survival [23,37]. Two studies, which compared high levels of proteinuria (more than 0.3 or 0.5 g/ day), found no deleterious effect on SCr or GL [25,26].

Ten different studies analyzed the influence of pre-pregnancy SCr on graft outcomes (SCr post-pregnancy and GL or graft survival). Multiple different cut-off values were described among these studies, ranging from SCr >1.47 mg/dL to 2.26 mg/dL and >1.0 mg/dL to 2.1 mg/dL [18,23-26,28,29,31,32]. Ten studies found a negative effect on graft function in patients with high SCr prior to pregnancy. Eight of them used SCr >1.47 mg/dL as cut of point [18,23,25,28-32], one study defined worse graft function as >1.24 mg/dL, two of them used no cutoff point where one described a negative effect of worse graft function (OR 1.71, 95% CI [1.15-3.45], p = 0.04) [22] and one found no relationship between pre pregnancy SCr and GL (OR - 0.11, 95% CI [-0.44-0.23], p = 0.52). Two other studies used cut off points <2.26 mg/dl and <1.3 mg/dl also found no negative effect on post-pregnancy graft function in women with high SCr prior to pregnancy [26,27] (**Table 3**).

Preeclampsia as a risk factor for accelerated graft loss

The development of preeclampsia during pregnancy was mentioned by one study as factor for graft dysfunction during pregnancy [31]. Preeclampsia was defined as hypertension and proteinuria > 0,30 grams/24hr. One study showed that preeclampsia was a 'borderline' risk factor for graft loss (OR, 1.09; 95% CI [0.92-1.34] p =0.09) [22]. The latest matched cohort study did not see a relation between preeclampsia and graft loss [38].

Transplant to conception interval as a risk factor for accelerated graft loss

The relationship between transplant to conception interval (TCI) and graft function is reported by five individual studies, which report on different outcomes of TCI (in general, TCI < 1 yr, TCI <2 yr, TCI >5 yr) [3,16,19,32,33]. Stoumpos et al. found no negative relationship between graft function and TCI [3]. One study found more graft loss in patients with TCI less than one year [32], whereas another study found no significant impact on graft outcome [19]. In another study there was no adversely effect on graft survival in patients with TCI less than two year, compared to other subgroups [16]. A TCI of more than five years has acceptable outcomes on post-pregnancy graft function and rejection during pregnancy and up to three months postpartum [33].

Assessment of quality and publication bias

We assessed study quality with the use of critical appraisal on applicability and validity (Appendix 2). Seventeen studies had a sample size of less than 20 women. Missing data was not well described in 21 of the studies. Ten studies did not describe their statistical analysis precisely. In six studies possible confounding factors were not mentioned in the article. Publication bias for studies on GL is unlikely as GL funnel-plot shows symmetry (Appendix 3)**.** There is a funnel-plot asymmetry in the subgroup of Δ SCr <2 years after pregnancy indicating publication bias towards the publication of small studies with positive delta SCr values (Appendix 4A).

DISCUSSION

In this meta-analysis and systematic review, we aimed to investigate the effect of pregnancy on long-term graft survival and function as guidance for pre-conceptional counseling using data derived from 42 studies. This meta-analysis gives an update on GL after pregnancy after KT. It includes cohort studies with nulliparous control groups and pooled data on graft function after pregnancy after KT. We are the first to analyze pooled data on long-term SCr after pregnancy in KT recipients. GL and SCr after pregnancy in KT recipients are reassuring with no difference in GL when compared to nulliparous KT recipients and stable SCr up to 10 years postpartum. We only found a slight significant rise in SCr in the period within two years after delivery of 0.18 mg/dL of which it can be discussed if such a small increase is clinically relevant, especially since Δ SCr was not increased at later time points after pregnancy.

The present meta-analysis added more than 500 women from twenty-three additional studies to the literature since the last meta-analysis from 2011 on the subject [1]. We report slightly higher outcomes on GL within two years (9,4% versus 8%), and higher numbers of GL of 22,3% versus 19% after five to ten years post-pregnancy, this was mainly caused by the TPR report [2]. Desphande reported 12.5 year post-pregnancy GL of 11%, based on one study of Gorgulu [39]. We could not include this study in our meta-analysis because they only reported on GL after KT and not on GL after pregnancy. Our outcome of GL of 38.5% more than ten-year post-partum is based on a pooled incidence of five new studies [14,20-22,29].

We added ten studies that compared the result of GL after KT with a nulliparous KT control group. The absence of a difference in GL between parous and nulliparous is reassuring. We ascertained that the control groups used were heterogenic among the studies: almost all studies were age and SCr before conception matched. The question remains whether the used control groups are really comparable because

the reason they did not conceive might be the result of other underlying conditions, which also can influence SCr and GL.

This study provides us insight into incidence of GL per years postpartum. It would have been informative to perform the same analyses per years post-transplant. Unfortunately, post-transplant years were rarely reported, which restricted us from performing this analysis. Therefore, it is hard to compare our results with the GL numbers from the registries. When comparing GL results after pregnancy to the age group of 16-34 years (men and women) of the Eurotransplant region, the number of GL after pregnancy are lower than the number of GL after KT in the general KT population. Ten years GL after KT (living and post mortal donors) is 46% and fifteen years GL is 60% for this age group in the Eurotransplant region [40]. This finding of relatively good graft survival in women with pregnancy after KT is reassuring. Although the argument that KT recipients with worse renal and physical condition are less likely to get pregnant also counts for this comparison.

In addition to previous meta-analysis [1], we examined long-term graft function after pregnancy in KT recipients. A small significant rise in SCr within two years after delivery as described in 87 KT recipients derived from three studies [29,41,42]. Possibly, this might be caused by physiological changes after pregnancy or restart of medication such as ACE inhibitors. On the other hand, this could be the result of high rate of risk factors in the study population (65.9% hypertension, 36.5% SCr >1.5mg/dL prior to pregnancy [29]) which makes these women more prone for deterioration of graft function or even GL. Most importantly, we do not find an increase in SCr during the period 5 years after pregnancy. However, women with a malfunctioning graft or lost to follow-up are not present in subgroups longer time after pregnancy possibly inducing bias. This is in line with the recent systematic review on the effect of pregnancy in chronic kidney disease, which reported no shift in CKD stage after pregnancy [43].

Risk factors for GL after pregnancy in KT were hypertension, proteinuria, transplant to conception/delivery interval and preconception graft function. However, only a few of the studies reporting on these risk factors performed a multivariate analysis, influenced by power. It is difficult to establish cause-relationship effects of risk factors. These risk factors are mentioned in the European and American guidelines, aiming at improving outcome in KT recipients [10,44]. The TCI is a point of discussion as it was stated by the European guidelines for two years after KT. The American guidelines changed their advice to postpone pregnancy at least until one year after pregnancy. Studies such as Fischer and Pour Reza Gholi showed reassuring results of pregnancies after one year after pregnancy[16,19]. Pregnancy within one year after KT is associated with an increased risk on GL, which Rose et al showed

in their recent study [45]. Data on the association of preeclampsia with GL show confliction results [31,34,38].

The strength of our meta-analysis is that we pooled data on GL including studies with a nulliparous control group and for the first time examined pooled incidences of graft function post-pregnancy. One of the limitations of this study is that the quality of some studies was poor with small sample size. The funnel plot analysis in the subgroup of Δ SCr 24 months after pregnancy showed an asymmetry, possibly publication bias is present (Appendix 4A). In addition, this is an unadjusted meta-analysis in which we could not account for factors such as differences in health care systems or socio-economic status or difference in SCr measurements because of lack of such information.

Unfortunately, we were not able to perform a meta-analysis on eGFR (estimated Glomerular Filtration Rate). Most studies only report SCr without age, calculation of eGFR was not possible [46]. We assumed that pre-conceptional creatinine was really pre-conceptional as it was stated in the text. It could be possible that the pre-conceptional SCr that was used for the included studies were not completely pre-conceptional and that the SCr was already physiologically increased. Ultimately evaluation of individual slope of eGFR pre- and post-pregnancy would be performed by means of a multi-levels analysis to answer the question whether pregnancy has effect on longer term GFR. Additionally, it would be possible to identify the most important predictors for worse graft outcomes after pregnancy after KT in relation to eGFR slope change.

In conclusion, this systematic review and meta-analysis showed a possible association with short term SCr decline post-partum, but no association at longer periods of time after delivery. The incidence of GL up to 10 years post pregnancy is limited but data analyzed show reassuring data on GL with pregnancy after KT compared to nulliparous controls and age-matched and SCr matched controls. This should be taken into consideration during pre-conceptional counseling. Based on risk factors for graft loss it could be concluded that if pre-pregnancy KT function is good, it remains good after pregnancy. Systematic review of the literature showed that mainly pre-pregnancy proteinuria, hypertension and high SCr are risk factors for GL.

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References

1. Deshpande NA JN, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Montgomery RA, Segev DL. Pregnancy Outcomes in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis. *American Journal of Transplantation.* 2011.
2. Moritz MJ CS, Coscia LA, et al. Transplant Pregnancy Registry International (TPR). *2017 annual report.* Philadelphia PA: Gift of Life Institute; 2018:0-21.
3. Stoumpos S, McNeill SH, Gorrie M, et al. Obstetric and long-term kidney outcomes in renal transplant recipients: a 40-yr single-center study. *Clin Transplant.* 2016;30(6): 673-681.
4. Sibanda N BJ, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: A report from the UK transplant registry. *Transplantation.* 2007;83(10): 1301-1307.
5. Chittka D, Hutchinson JA. Pregnancy After Renal Transplantation. *Transplantation.* 2017;101(4): 675-678.
6. Davison JM. The effect of pregnancy on kidney function in renal allograft recipients. *Kidney Int.* 1985;27(1): 74-79.
7. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. *Br J Obstet Gynaecol.* 1981;88(1): 1-9.
8. Richman K, Gohh R. Pregnancy after renal transplantation: a review of registry and single-center practices and outcomes. *Nephrol Dial Transplant.* 2012;27(9): 3428-3434.
9. McKay DB, Josephson MA. Reproduction and Transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. *American Journal of Transplantation.* 2005;5(7): 1592-1599.
10. Transplantation EEGoR. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant.* 2002;17 Suppl 4: 50-55.
11. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5: 13.
12. *Statistical analysis: Microsoft Excel 2010* [computer program]. Indianapolis: QUE 2011.
13. *Review Manager (RevMan) [Computer Program]* [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
14. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J Am Soc Nephrol.* 2009;20(11): 2433-2440.
15. First MR, Combs CA, Weiskittel P, Miodovnik M. Lack of effect of pregnancy on renal allograft survival or function. *Transplantation.* 1995;59(4): 472-476.
16. Fischer T, Neumayer HH, Fischer R, et al. Effect of pregnancy on long-term kidney function in renal transplant recipients treated with cyclosporine and with azathioprine. *Am J Transplant.* 2005;5(11): 2732-2739.
17. Kashanizadeh N, Nemati E, Sharifi-Bonab M, et al. Impact of pregnancy on the outcome of kidney transplantation. *Transplant Proc.* 2007;39(4): 1136-1138.
18. Kim HW, Seok HJ, Kim TH, Han DJ, Yang WS, Park SK. The experience of pregnancy after renal transplantation: pregnancies even within postoperative 1 year may be tolerable. *Transplantation.* 2008;85(10): 1412-1419.

19. Pour-Reza-Gholi F, Nafar M, Farrokhi F, et al. Pregnancy in kidney transplant recipients. *Transplant Proc.* 2005;37(7): 3090-3092.
20. Rahamimov R, Ben-Haroush A, Wittenberg C, et al. Pregnancy in renal transplant recipients: long-term effect on patient and graft survival. A single-center experience. *Transplantation.* 2006;81(5): 660-664.
21. Sturgiss SN, Davison JM. Effect of pregnancy on the long-term function of renal allografts: an update. *Am J Kidney Dis.* 1995;26(1): 54-56.
22. Svetitsky S, Baruch R, Schwartz IF, et al. Long-Term Effects of Pregnancy on Renal Graft Function in Women After Kidney Transplantation Compared With Matched Controls. *Transplant Proc.* 2018;50(5): 1461-1465.
23. Queipo-Zaragoza JA, Vera-Donoso CD, Soldevila A, Sanchez-Plumed J, Broseta-Rico E, Jimenez-Cruz JF. Impact of pregnancy on kidney transplant. *Transplant Proc.* 2003;35(2): 866-867.
24. Kato M, Hattori R, Kinukawa T, Kamihira O, Yamada S, Gotoh M. Correlation between treated hypertension in prepregnancy and transplanted kidney function deterioration during pregnancy even if within pregnancy permission criteria. *Transplant Proc.* 2012;44(3): 635-637.
25. Thompson BC KE, Tuck SM, Fernando ON, Sweny P. Pregnancy in renal transplant recipients: the Royal Free Hospital experience. *Q J Med.* 2003;96: 837-844.
26. Rocha A, Cardoso A, Malheiro J, et al. Pregnancy after kidney transplantation: graft, mother, and newborn complications. *Transplant Proc.* 2013;45(3): 1088-1091.
27. Hooi LS, Rozina G, Shaariah MY, et al. Pregnancy in patients with renal transplants in Malaysia. *Med J Malaysia.* 2003;58(1): 27-36.
28. O'Reilly B, Compton F, Ogg C, Pattison J, Maxwell D. Renal function following pregnancy in renal transplant recipients. *J Obstet Gynaecol.* 2001;21(1): 12-16.
29. Keitel E, Bruno RM, Duarte M, et al. Pregnancy outcome after renal transplantation. *Transplantation Proceedings.* 2004;36(4): 870-871.
30. Crowe AV, Rustom R, Gradden C, et al. Pregnancy does not adversely affect renal transplant function. *QJM.* 1999;92(11): 631-635.
31. Aivazoglou L, Sass N, Silva HT, Jr., Sato JL, Medina-Pestana JO, De Oliveira LG. Pregnancy after renal transplantation: an evaluation of the graft function. *Eur J Obstet Gynecol Reprod Biol.* 2011;155(2): 129-131.
32. Alfi AY, Al-essawy MA, Al-lakany M, Somro A, Khan F, Ahmed S. Successful pregnancies post renal transplantation. *Saudi J Kidney Dis Transpl.* 2008;19(5): 746-750.
33. Gaughan WJ, Moritz MJ, Radomski JS, Burke JF, Jr., Armenti VT. National Transplantation Pregnancy Registry: report on outcomes in cyclosporine-treated female kidney transplant recipients with an interval from transplant to pregnancy of greater than five years. *Am J Kidney Dis.* 1996;28(2): 266-269.
34. Abe T, Ichimaru N, Okumi M, et al. Pregnancy after renal transplantation: a single-center experience. *Int J Urol.* 2008;15(7): 587-592.
35. Ajaimy M, Lubetzky M, Jones T, et al. Pregnancy in sensitized kidney transplant recipients: a single-center experience. *Clin Transplant.* 2016;30(7): 791-795.
36. Ghafari A, Sanadgol H. Pregnancy after renal transplantation: ten-year single-center experience. *Transplant Proc.* 2008;40(1): 251-252.

37. Fernandez-Fresnedo G, Plaza JJ, Sanchez-Plumed J, Sanz-Guajardo A, Palomar-Fontanet R, Arias M. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. *Nephrol Dial Transplant.* 2004;19 Suppl 3: iii47-51.

38. Vannevel V, Claes K, Baud D, et al. Preeclampsia and Long-term Renal Function in Women Who Underwent Kidney Transplantation. *Obstet Gynecol.* 2018;131(1): 57-62.

39. Gorgulu N, Yelken B, Caliskan Y, Turkmen A, Sever M. Does pregnancy increase graft loss in female renal allograft recipients? *Clinical and Experimental Nephrology.* 2010;14(3): 244-247.

40. Eurotransplant. 2018.(derived from www.eurotransplant.org)

41. Candido C, Cristelli MP, Fernandes AR, et al. Pregnancy after kidney transplantation: high rates of maternal complications. *J Bras Nefrol.* 2016;38(4): 421-426.

42. Kwek JL, Tey V, Yang L, Kanagalingam D, Kee T. Renal and obstetric outcomes in pregnancy after kidney transplantation: Twelve-year experience in a Singapore transplant center. *J Obstet Gynaecol Res.* 2015;41(9): 1337-1344.

43. Piccoli GB, Cabiddu G, Attini R, et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. *J Am Soc Nephrol.* 2015;26(8): 2011-2022.

44. McKay DB, Josephson MA, Armenti VT, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant.* 2005;5(7): 1592-1599.

45. Rose C, Gill J, Zalunardo N, Johnston O, Mehrotra A, Gill JS. Timing of Pregnancy After Kidney Transplantation and Risk of Allograft Failure. *Am J Transplant.* 2016;16(8): 2360-2367.

46. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis.* 2010;55(4): 622-627.

47. Amine BHH, Haythem S, Kais H, Radhouane R. Pregnancy after renal transplantation: a retrospective study at the military hospital of Tunis from 1992 to 2011. *Pan Afr Med J.* 2017;28: 137.

48. Areia A, Galvao A, Pais MS, Freitas L, Moura P. Outcome of pregnancy in renal allograft recipients. *Arch Gynecol Obstet.* 2009;279(3): 273-277.

49. Basaran O, Emiroglu R, Secme S, Moray G, Haberal M. Pregnancy and renal transplantation. *Transplant Proc.* 2004;36(1): 122-124.

50. Debska-Slizien A, Galgowska J, Chamienia A, et al. Pregnancy after kidney transplantation: a single-center experience and review of the literature. *Transplant Proc.* 2014;46(8): 2668-2672.

51. Di Loreto P, Martino F, Chiaramonte S, et al. Pregnancy after kidney transplantation: two transplantation centers--Vicenza-Udine experience. *Transplant Proc.* 2010;42(4): 1158-1161.

52. El Houssni S, Sabri S, Benamar L, Ouzeddoun N, Bayahia R, Rhou H. Pregnancy after renal transplantation: Effects on mother, child, and renal graft function. *Saudi J Kidney Dis Transpl.* 2016;27(2): 227-232.

53. Farr A, Bader Y, Husslein PW, Gyori G, Muhlbacher F, Margreiter M. Ultra-high-risk pregnancies in women after renal transplantation. *Eur J Obstet Gynecol Reprod Biol.* 2014;180: 72-76.

54. Galdo T, Gonzalez F, Espinoza M, et al. Impact of pregnancy on the function of transplanted kidneys. *Transplant Proc.* 2005;37(3): 1577-1579.

55. Gorgulu N, Yelken B, Caliskan Y, Turkmen A, Sever MS. Does pregnancy increase graft loss in female renal allograft recipients? *Clin Exp Nephrol.* 2010;14(3): 244-247.

56. Hebral AL, Cointault O, Connan L, et al. Pregnancy after kidney transplantation: outcome and anti-human leucocyte antigen alloimmunization risk. *Nephrol Dial Transplant.* 2014;29(9): 1786-1793.
57. Little MA, Abraham KA, Kavanagh J, Connolly G, Byrne P, Walshe JJ. Pregnancy in Irish renal transplant recipients in the cyclosporine era. *Ir J Med Sci.* 2000;169(1): 19-21.
58. Melchor JL, Gracida C, Sanmartin MA. Kidney transplantation and pregnancy in a Mexican women sample. *Transplant Proc.* 2002;34(1): 361-362.
59. Salmela K, Kyllonen L, Holmberg C, Gronhagen-Riska C. Influence of pregnancy on kidney graft function. *Transplant Proc.* 1993;25(1 Pt 2): 1302.
60. Yassaee F, Moshiri F. Pregnancy outcome in kidney transplant patients. *Urol J.* 2007;4(1): 14-17.
61. Yildirim Y, Uslu A. Pregnancy in patients with previous successful renal transplantation. *Int J Gynaecol Obstet.* 2005;90(3): 198-202.

Supplemental material

Appendix 1. Search syntax Pubmed, Embase, Cochrane.

Domain Pubmed	Embase	Cochrane
((((((kidney[MeSH Terms]) OR kidney[Title/Abstract]) OR renal[Title/Abstract])) AND ((((((((transplant) OR transplantation[Title/Abstract]) OR transplantations[Title/Abstract]) OR allotransplant[Title/Abstract]) OR allotransplantation[Title/Abstract]) OR allotransplantations[Title/Abstract]) OR graft*[Title/Abstract]) OR allograft*[Title/Abstract])))) OR kidney transplantation[MeSH Terms]	renal:ab,ti OR kidney:ab,ti OR kidneys:ab,ti AND ('transplantation'/exp OR transplant:ab,ti OR transplantation:ab,ti OR transplantations:ab,ti OR allotransplant:ab,ti OR allotransplants:ab,ti OR graft:ab,ti OR grafting:ab,ti OR allograft:ab,ti OR allografts:ab,ti) OR 'kidney transplantation':ab,ti OR 'kidney transplantation'/exp	renal:ti,ab OR kidney:ti,ab OR kidneys:ti,ab AND (transplant:ti,ab OR transplantation:ti,ab OR transplantations:ti,ab OR allotransplant:ti,ab OR allotransplants:ti,ab OR graft:ti,ab OR grafting:ti,ab OR allograft:ti,ab OR allografts:ti,ab) OR 'kidney transplantation':ti,ab
Determinant Pubmed	Embase	Cochrane
(((((((pregnancy[MeSH Terms]) OR pregnant[Title/Abstract]) OR pregnancy[Title/Abstract]) OR pregnancies[Title/Abstract]) OR gestation[Title/Abstract]) OR gestational[Title/Abstract]) OR gravid[Title/Abstract]) OR gravidity[Title/Abstract]) OR gravidities[Title/Abstract]	pregnant:ab,ti OR pregnancy:ab,ti OR pregnancies:ab,ti OR gestation:ab,ti OR gestational:ab,ti OR childbearing:ab,ti OR 'child bearing':ab,ti OR gravidity:ab,ti OR 'pregnant'/exp	pregnant:ti,ab OR pregnancy:ti,ab OR pregnancies:ti,ab OR gestation:ti,ab OR gestational:ti,ab OR childbearing:ti,ab OR "child bearing":ti,ab OR gravidity:ti,ab
Outcome pubmed	Embase	Cochrane
(((((((Renal[Title/Abstract]) OR kidney[Title/Abstract])) AND ((((((((((((((((((function[Title/Abstract]) OR functions[Title/Abstract]) OR "function decline"[Title/Abstract]) OR "function declining"[Title/Abstract]) OR "function decrease"[Title/Abstract]) OR "function decreased"[Title/Abstract]) OR "function decreases"[Title/Abstract]) OR Failure[Title/Abstract]) OR Failures[Title/Abstract]) OR Insufficient[Title/Abstract]) OR Insufficiency[Title/Abstract]) OR Insufficiencies[Title/Abstract]) OR "graft survival"[Title/Abstract]) OR "graft loss"[Title/Abstract]) OR "graft survivals"[Title/Abstract]) OR "Graft function"[Title/Abstract]) OR "Graft failure"[Title/Abstract]) OR "allograft survival"[Title/Abstract]) OR "allograft survivals"[Title/Abstract])))) AND ((((((((((((((((((((renal insufficiency[MeSH Terms]) OR "Glomerular filtration rate"[Title/Abstract]) OR "Glomerular filtration rates"[Title/Abstract]) OR "Glomerular filtration rate slope"[Title/Abstract]) OR "GFR slope"[Title/Abstract]) OR "GFR slopes"[Title/Abstract]) OR "eGFR slope"[Title/Abstract]) OR "eGFR slopes"[Title/Abstract]) OR GFR[Title/Abstract]) OR eGFR[Title/Abstract]) OR e-GFR[Title/Abstract]) OR Creatinin[Title/Abstract]) OR Creatinine[Title/Abstract]) OR "serum creatinine"[Title/Abstract]) OR MDRD[Title/Abstract]) OR "Cockroft Gault"[Title/Abstract]) OR "modification of diet in renal disease"[Title/Abstract]) OR Inulin[Title/Abstract]) OR Iothalamat[Title/Abstract]) OR "Cystatin C"[Title/Abstract] OR "CKD epi"[Title/Abstract]) OR Proteinuria[Title/Abstract]) OR Proteinuria[MeSH Terms]) OR Albuminuria[Title/Abstract]) OR Albuminuria[MeSH Terms]) OR Microalbuminuria[Title/Abstract]) OR Macroalbuminuria[Title/Abstract]))))))	((renal:ab,ti OR kidney:ab,ti) AND (function:ab,ti OR functions:ab,ti OR 'function decline':ab,ti OR 'function declining':ab,ti OR 'function decrease':ab,ti OR 'function decreased':ab,ti OR 'function decreases':ab,ti OR failure:ab,ti OR failures:ab,ti OR insufficient:ab,ti OR insufficiency:ab,ti OR insufficiencies:ab,ti OR 'graft survival':ab,ti OR 'graft loss':ab,ti OR 'graft survivals':ab,ti OR 'graft function':ab,ti OR 'graft failure':ab,ti OR 'allograft survival':ab,ti OR 'allograft survivals':ab,ti)) OR 'renal insufficiency':ab,ti OR 'glomerulus filtration rate':ab,ti OR 'glomerulus filtration rates':ab,ti OR 'glomerulus filtration rate slope':ab,ti OR 'gfr slope':ab,ti OR 'gfr slopes':ab,ti OR 'egfr slope':ab,ti OR 'egfr slopes':ab,ti OR gfr:ab,ti OR egfr:ab,ti OR 'e gfr':ab,ti OR creatinin:ab,ti OR creatinine:ab,ti OR 'serum creatinine':ab,ti OR 'creatinine blood level':ab,ti OR 'serum creatinin':ab,ti OR mdrd:ab,ti OR 'cockroft gault':ab,ti OR 'modification of diet in renal disease':ab,ti OR inulin:ab,ti OR iothalamat:ab,ti OR 'cystatin c':ab,ti OR 'ckd epi':ab,ti OR proteinuria:ab,ti OR 'proteinuria'/exp OR albuminuria:ab,ti OR 'albuminuria'/exp OR microalbuminuria:ab,ti OR macroalbuminuria:ab,ti	((renal:ti,ab or kidney:ti,ab) and (function:ti,ab or functions:ti,ab or "function decline":ti,ab or "function declining":ti,ab or "function decrease":ti,ab or "function decreased":ti,ab or "function decreases":ti,ab or failure:ti,ab or failures:ti,ab or insufficient:ti,ab or insufficiency:ti,ab or insufficiencies:ti,ab or "graft survival":ti,ab or "graft loss":ti,ab or "graft survivals":ti,ab or "graft function":ti,ab or "graft failure":ti,ab or "allograft survival":ti,ab or "allograft survivals":ti,ab)) or "renal insufficiency":ti,ab or "glomerular filtration rate":ti,ab or "glomerular filtration rates":ti,ab or "glomerular filtration rate slope":ti,ab or "gfr slope":ti,ab or "egfr slope":ti,ab or gfr:ti,ab or egfr:ti,ab or "e gfr":ti,ab or creatinin:ti,ab or creatinine:ti,ab or "serum creatinine":ti,ab or "serum creatinin":ti,ab or mdrd:ti,ab or "cockroft gault":ti,ab or "modification of diet in renal disease":ti,ab or inulin:ti,ab or iothalamat:ti,ab or "cystatin c":ti,ab or "ckd epi":ti,ab or proteinuria:ti,ab or albuminuria:ti,ab or microalbuminuria:ti,ab or macroalbuminuria:ti,ab

Appendix 2. Critical appraisal of topic table

Author (year) Journal	General		Applicability		Validity					
	Study design	Study size (n=)	Domain	Determinant	Outcome: PP renal function Graft loss	Missing data	Loss to follow up	Standardization of outcome	Analysis	Confounding	Data extraction PP renal function Graft loss
Abe (2008) International Journal of Urology	scRCS	20	●	●	●◗	●	●	◗	◗	◗	●●
Aivazoglou (2010) European Journal of Obstetrics & Gynecology and Reproductive Biology	scPCS	31	●	●	●●	●	◗	◗	●	◗	●●
Ajaimy (2016) American journal of Transplantation	scRCS	11	●	●	○●	○	●	●	○	●	○●
Alfi (2008) Saudi Journal of Kidney Disease and Transplantation	scRCS	12	●	●	●●	●	◗	●	●	●	●●
Amine (2017) PanAfrican Medical Journal	scRCs	12	●	●	◗○	●	○	◗	○	◗	○●
Areia (2009) Arch Gynecol Obstet	scRCS	28	●	●	●●	◗	○	●	●	●	●○
Basaran (2005) Transplantation Proceedings	scRCS	8	●	●	◗●	○	●	◗	○	◗	●●
Candido (2016) Journal Brasilian Nefrology	scRCs	36	●	●	●●	●	●	◗	◗	◗	●●

Crowe (1999) Quarterly Journal of Medicine	scRCS	29	◗	●	●●	●	○	●	◗	◗	●○
Debska-Slizien (2014) Transplantation Proceedings	scRCS	17	●	●	●●	○	●	●	●	◗	○●
Di Loreto (2010) Transplant Proceedings	scRCS	12	●	●	○●	○	○	◗	○	●	○●
El Houssni (2016) Transplant International	scRCS	12	●	●	○●	●	●	●	●	●	○●
Farr (2014) European journal of obstetrics and gynaecology and reproductive biology	scRCS	10	◗	●	●●	●	●	●	●	●	●●
First (1995) Transplantation	scCRCS	18	●	●	○●	○	○	◗	◗	◗	○●
Fischer (2005) American Journal of Transplantation	mcCRCS	81	●	●	○◗	●	●	◗	●	◗	○●
Galdo (2005) Transplantation Proceedings	scRCS	30	●	●	●○	○	○	●	◗	◗	●○
Gaughan (1996) American journal of kidney diseases	mcRCS	15	◗	●	●●	◗	●	◗	◗	◗	○●
Ghafari (2008) Transplantation proceedings	scRCS	53	●	●	○●	○	◗	◗	◗	◗	○●
Gorgulu (2010) Clinical and Experimental Nephrology	scRCS	19	●	●	●◗	○	●	●	◗	○	●○
Hebral (2014) Nephrology Dialysis Transplantation	scRCS	46	●	●	●●	◗	◗	●	◗	●	○●
Hooi (2003) Medical Journal of Malaysia	mcRCS	46	●	●	●◗	◗	●	●	●	●	●●
Kashanizadeh (2007) Transplantation Proceedings	scCRCS	86	●	●	○●	○	●	●	◗	◗	○●
Kato (2012) Transplantation Proceedings	mcRCS	23	●	●	●●	○	○	●	◗	○	●●
Keitel (2004) Transplantation Proceedings	scRCS	41	●	●	●◗	○	●	●	◗	○	●●
Kim (2008) Transplantation	scCRCS	48	●	●	○●	○	○	●	●	●	○●
Kwek (2015) Journal of Obstetrics and Gynaecolgoy Research	scRCS	10	●	●	●●	●	●	●	●	●	●●
Levidiotis (2009) Journal of American Society of Nephrology	scCRCS	118	●	●	●●	●	●	◗	◗	◗	○●
Little (2000) Irish Journal of Medicine Science	scRCS	19	◗	●	●●	○	●	●	○	○	●●
Melchor (2002) Transplantionn Proceedings	scRCS	21	●	●	○●	○	●	◗	○	○	○●
Moritz (2018) Annual Report International Pregnancy Transplantation Registry	mcRCS	1100	●	●	●●	○	○	◗	◗	◗	○●
O'Reilly (2001) Journal of Obstetrics and Gynaecology	scRCS	41	◗	●	●●	○	●	●	◗	◗	○●

	Study design	Study size	Domain	Determinant	Outcome	Missing data	Loss to follow up	Standardization of outcome	Analysis	Confounding	Data extraction
Pour-Reza Gholi (2005) Transplantation proceedings	scCRCS	60	●	●	◗●	◗	○	◗	◗	◗	○●
Rahaminov (2006) Transplantation	scCRCS	39	●	●	○●	○	○	◗	◗	◗	○●
Queipo-Zaragoza (2003) Transplantation proceedings	scRCS	29	●	●	●●	○	●	●	○	◗	○●
Salmela (1993) Transplantation	scRCS	22	●	●	●●	○	●	●	◗	◗	○●
Sibanda (2007) Transplantation	mcCRCS	176	●	●	○●	◗	○	●	◗	◗	○●
Stoumpos (2016) Clinical transplantation	scCRCS	83	●	●	●○	●	●	●	●	●	●○
Sturgiss (1995) American Journal of Kidney disease	scCRCS	18	●	●	●●	○	●	●	●	◗	●●
Svetitsky (2018) Transplant Proceedings	scRCS	18	●	●	●●	●	○	○	◗	●	●●
Thompson (2003) Quarterly Journal of Medicine	scCRCS	24	●	●	●●	◗	○	●	○	●	●●
Vannevel (2018) Obstetrics & Gyneacology	mcRCS	52	●	●	◗●	◗	◗	●	●	●	○●
Yassaee (2007) Urol Journal	mcRCS	74	●	●	○●	○	○	●	○	○	○●
Yildirim (2005) International Journal of Gynecology and Obstetrics	scRCS	17	●	●	●●	●	●	●	○	◗	●●

Legend CAT Table

General

Study design: single center (sc), multicenter (mc), prospective cohort study (PCS), retrospective cohort study (RCS), retrospective cohort study with control group (CRCS)

Study size: number of kidney transplant recipients who became pregnant after kidney transplantation (KT) n = number of pregnancies.

Applicability

Domain: ●: KT; ◗: subgroup analysis within KT recipients; ○: other domain reported

Determinant: ●: pregnancy with renal allograft.

Outcome: ●: post-pregnancy KT function, graft loss both with a follow up post-pregnancy of more than 6 months; ◗: graft survival; ○: no description of post-pregnancy KT function or graft loss/graft survival.

Validity

Missing data: ●: ≤10% missing and non-selective; ◗: >10% missing data, but a sensitivity analysis was conducted to account for those missings; ○: >10% missing data, selective or not reported.

Loss to follow up: ●: Sufficient duration of follow up and well described, ≤10% loss to follow up and non-selective; ○: no duration of follow up described, >10% loss to follow up, selective or not described.

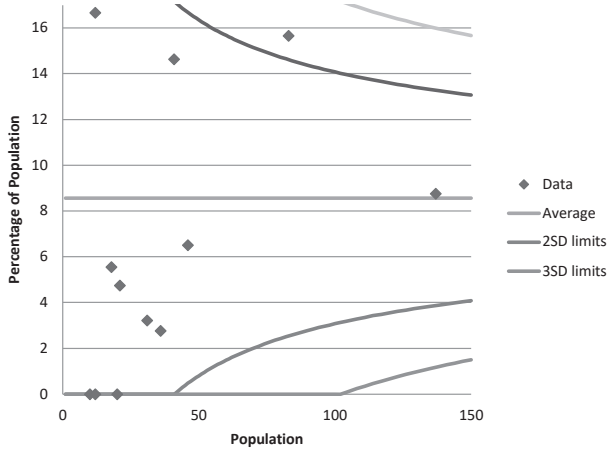
Standardization of outcome: ●: outcomes are clearly defined (SCr at a fixed time of follow up, eGFR (described which formula they used) at a fixed time in follow up, graft loss at fixed time of follow up; ◗: outcomes mentioned, but not clearly described (SCr reported, without clear description of follow up duration. eGFR reported, without clear description of follow up duration or no formula reported. Graft loss reported, without clear description of follow up duration or graft survival reported. ○: not well described.

Analysis: ●: correct and well reported use of statistical tests; ◗: summary description of used tests; ○: not well described

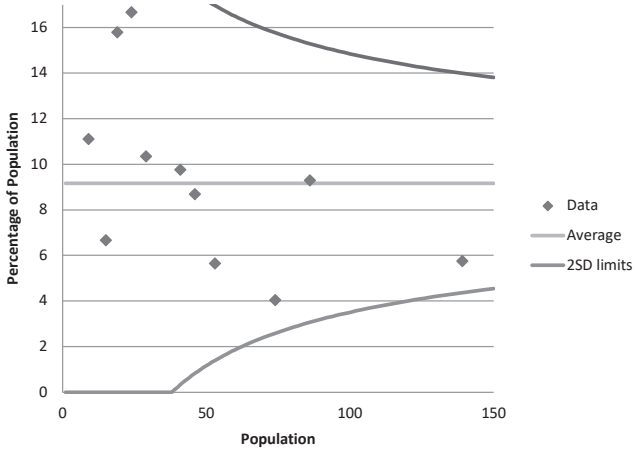
Confounding: ●: baseline characteristics described well (Reported characteristics of the study population such as BMI, ethnicity, smoking, cause of ESRD, duration of hemodialysis, age at KT, type of donor, use of immunosuppressants, TCI, age at delivery, etc); ◗: description of baseline characteristics, but general characteristics of the study population are missing (e.g. ethnicity, smoking, cause of ESRD); ○: no baseline characteristics reported.

Data extraction: ●: possible; ○: not possible

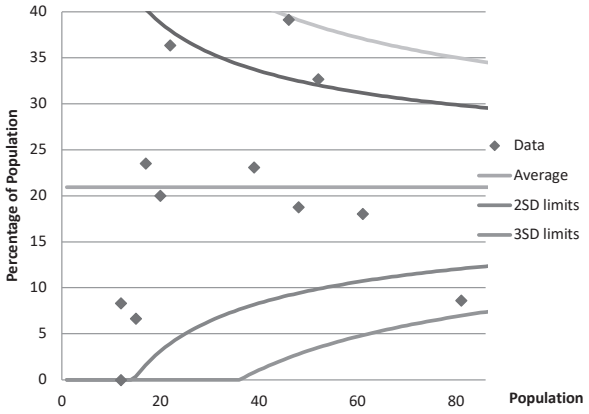
Appendix 3: Funnel plots for graft loss



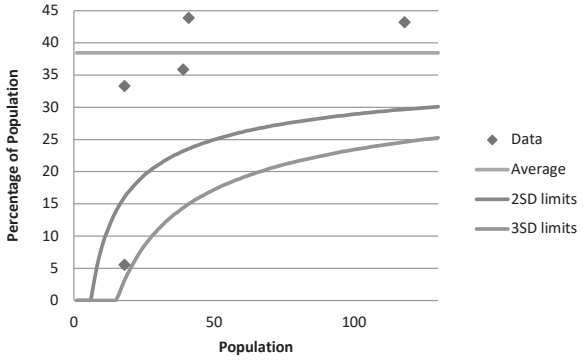
A: Graft loss < 2 years post pregnancy



B. Graft loss 2 – 5 years post pregnancy

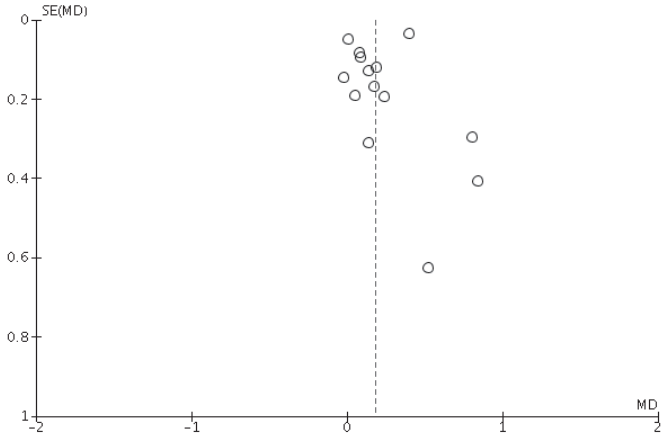


C. Graft loss 5-10 years post pregnancy

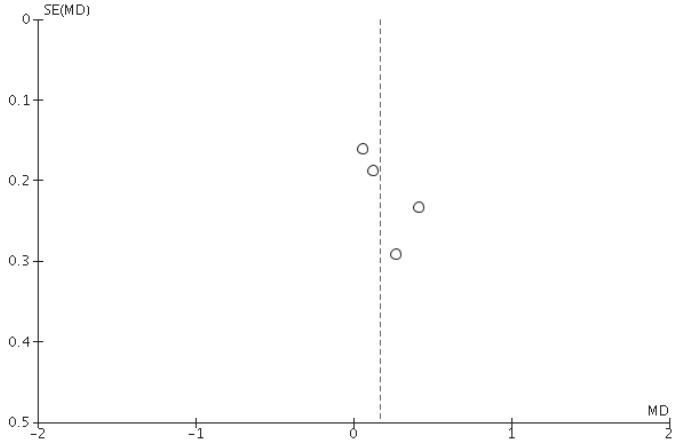


D. Graft loss > 10 years post pregnancy

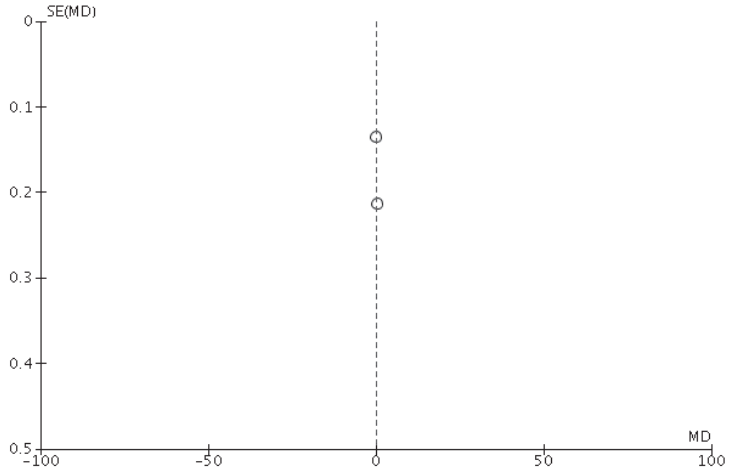
Appendix 4: Funnel plots SCr pre versus post pregnancy



4A: SCr pre versus 6m-2yr post pregnancy



4B: SCr pre versus 2-5 yr post pregnancy



4C: SCr pre versus >10 yr post pregnancy

Chapter 3

Effect of pregnancy on eGFR after kidney transplantation: a national cohort study

*Marleen C. van Buren, Margriet E. Gosselink , Henk Groen, Henk W. van Hamersvelt, Margriet de Jong, Martin H. de Borst, Robert Zietse, Jacqueline van de Wetering *, A. Titia Lely **

**Authors contributed equally*

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Effect of pregnancy on eGFR after Kidney Transplantation (KT)

Netherlands
1971-2017

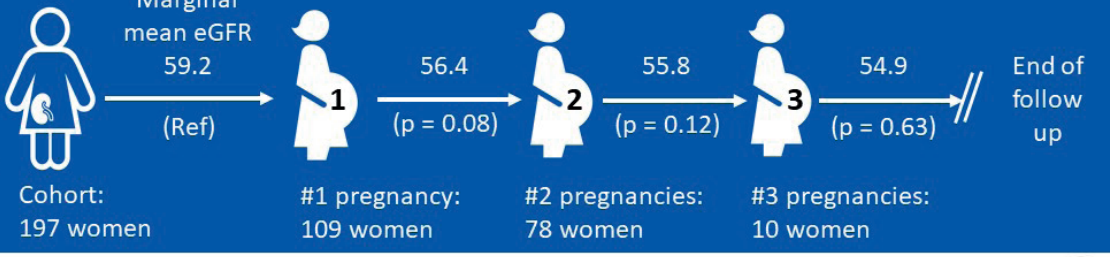
Retrospective cohort with KT
- Pregnancy (> 20 weeks)
- eGFR pre- & post- pregnancy

GEE multi-level analysis
- Women are their own controls
- Adjusted for transplant vintage

Conclusions
- Overall, pregnancy has no significant effect on eGFR post kidney transplantation
- A small but not significant drop in eGFR was seen following the 1st pregnancy

eGFR trajectories

3194 eGFR measurements
CKD-epi (ml/min/1.73m²)



Van Buren et al. *Transplantation*. May 2021

Transplantation

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ABSTRACT

Background

The effect of pregnancy on the course of estimated glomerular filtration rate (eGFR) is unknown in kidney transplant recipients (KT-recipients).

Methods

We conducted a nationwide multi-center cohort study in KT-recipients with pregnancy (>20 weeks) after kidney transplantation (KT). Annual eGFR's after KT until death or graft loss and additional eGFR's before each pregnancy were collected according to protocol. Changes in eGFR slope before and after each pregnancy were analyzed by generalized estimating equations (GEE) multilevel analysis adjusted for transplant vintage.

Results

We included 3194 eGFR measurements before and after pregnancy in 109 (55%) KT-recipients with one, 78 (40%) with two and 10 (5%) with three pregnancies after KT. Median follow-up after first delivery post-KT was 14 years (IQR 18 years). Adjusted mean eGFR pre-pregnancy was 59 ml/min/1.73m² (SEM 1.72; 95% CI 56-63), after first pregnancy 56 ml/min/1.73m² (SEM 1.70; 95% CI 53-60), after second pregnancy 56 ml/min/1.73m² (SEM 2.19; 95% CI 51-60) and after third pregnancy 55 ml/min/1.73m² (SEM 8.63; 95% CI 38-72). Overall eGFR slope after first, second and third pregnancy was not significantly worse than pre-pregnancy (p = 0.28). However, adjusted mean eGFR after first pregnancy was 2.8 ml/min/1.73m (p = 0.08) lower than pre-pregnancy.

Conclusions

First pregnancy has a small, but no significant, effect on eGFR slope in KT-recipients. Midterm hyperfiltration, a marker for renal reserve capacity, was associated with better eGFR and death-censored graft survival. In this KT cohort with long-term follow-up, no significant effect of pregnancy on kidney function was detected.

INTRODUCTION

Pregnancy after kidney transplantation (KT) is increasingly common. To date, the voluntary International Transplant Pregnancy Registry (TPR, USA) has registered more than 1100 pregnancies after KT [1]. There has been data that pregnancies may lead to higher risk of death-censored graft loss (DCGL) if there is presence of risk factors like creatinine greater than 1.5 mg/dl[2]. Nevertheless, the incidence of DCGL was not higher for kidney transplant recipients (KT-recipients) with a history of pregnancy than for nulliparous KT-recipients in multiple studies [3-12]. However, these studies used very heterogenic control groups and did not account for the fact nulliparous KT-recipients might have other underlying conditions such as syndromic disease which could also influence the choice of not conceiving or could affect the incidence of DCGL.

Besides post-pregnancy DCGL, little is known about the effect of pregnancy on the course of graft function in KT-recipients. Women with gestational hypertension show a decrease instead of the normal physiological increase in estimated glomerular filtration rate (eGFR) during pregnancy [13]. However, in these women the temporary decrease in eGFR during pregnancy did not persist or progress after pregnancy[14]. This physiological increase in eGFR during pregnancy is also known as midterm hyperfiltration. The absence of midterm hyperfiltration is related with worse pregnancy outcomes in the general population [15]. Bramham et al described an absence of SCr fall during pregnancy in almost 49% of KT-recipients, in this study no relationship with adverse pregnancy outcomes was found[16]. Whether midterm hyperfiltration during pregnancy has an effect on long-term eGFR in the KT population is unknown.

Recently, our meta-analysis amongst KT-recipients showed higher serum creatinine (SCr) from 6 until 24 months after pregnancy, compared with pre-pregnancy SCr[17]. However, this increase was not detectable beyond two years after pregnancy in several small studies [4,11,18-20]. Although reassuring, only one larger study addresses the effect of pregnancy on the long-term course of kidney function [11]. Therefore, we conducted an evaluation of individual eGFR slopes before and after pregnancy in a large nationwide KT cohort. Additionally, we identified the most important predictors for eGFR decline and DCGL following pregnancy after KT.

METHODS

For the collection of data, we used data from the Dutch PARTOUT network (Pregnancy After Renal Transplantation OUTcomes). This nationwide network consists of obstetricians and transplant nephrologists from all eight Dutch transplant centers and an epidemiologist. The study protocol, data management and analyses plan were designed within the multidisciplinary team of the PARTOUT network. All women who underwent a KT in the Netherlands since 1971 and became pregnant afterwards were included in this dataset. Data of KT as well as pregnancy outcomes were collected by examining the medical and obstetrical charts. Data was collected until December 31st, 2017. The PARTOUT study was approved by the Medical Ethics Committee of all transplant centers (MEC -2016-634, 16-021/C, G16.014, 2015-2262).

Selection of participants

Participants were identified by systemic search in the Dutch Organ Transplant Registry (NOTR). All patients transplanted in the Netherlands are registered in the NOTR. We complemented this by questioning nephrologists and gynecologists involved in pregnancy in KT-recipients of all transplant centers in the Netherlands. Of the 202 women identified with pregnancies after KT, 197 KT-recipients were included for analysis (**Figure 1**).

Data collection

Data collection, entry and access was organized by the PARTOUT network, using Open Clinica open source software[21]. The information required was obtained by thoroughly examining all available medical and obstetrical charts.

Baseline KT data included specifications of cause of end stage renal disease, type of KT, immunosuppressive and antihypertensive drug use, medical history. Rejection was defined as having a biopsy proven rejection or treatment for rejection by clinical diagnosis.

Furthermore, obstetric outcomes were collected. Pre-existing hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or antihypertensive drug use before pregnancy [22]. The same definition was used for pregnancy-induced hypertension for KT-recipients who developed hypertension during pregnancy without having pre-existing hypertension. Pre-eclampsia during pregnancy was not uniformly defined, since it was defined by the attending physician at the time of pregnancy. It could not be defined uniformly retrospectively due to the large number of missing proteinuria values. According to guidelines valid at that time, preeclampsia was marked by presence of pregnancy-induced hyperten-

sion, >20 weeks of gestation and proteinuria [23]. Midterm hyperfiltration was defined as having >15% decrease of SCr during pregnancy. This was calculated by comparing the lowest SCr between 8 and 20 weeks of gestation to pre-pregnancy SCr [24,25]. Proteinuria levels were unavailable for analysis due to missing data.

For the longitudinal analysis of kidney function, outpatient clinic SCr levels were collected after one year after KT (i.e., most recent pre-pregnancy KT) and every year thereafter until graft loss or death occurred or until the end of follow-up, which was December 31st, 2017. Additionally, SCr levels were collected at five consecutive time points before conception to ensure a sufficient amount of SCr levels were available before pregnancy. For each measurement, the exact interval after KT (in days) was calculated. A visual overview of the study design is presented in **Figure 2**. For this longitudinal analysis, SCr levels during pregnancy and within 6 months after delivery were excluded. Also, SCr measurements before the age of 18 years were excluded (pregnancy before the age of 18 did not occur). eGFR was calculated with the CKD-EPI formula (CKD epidemiology collaboration) and expressed in ml/min/1.73m^2 [26].

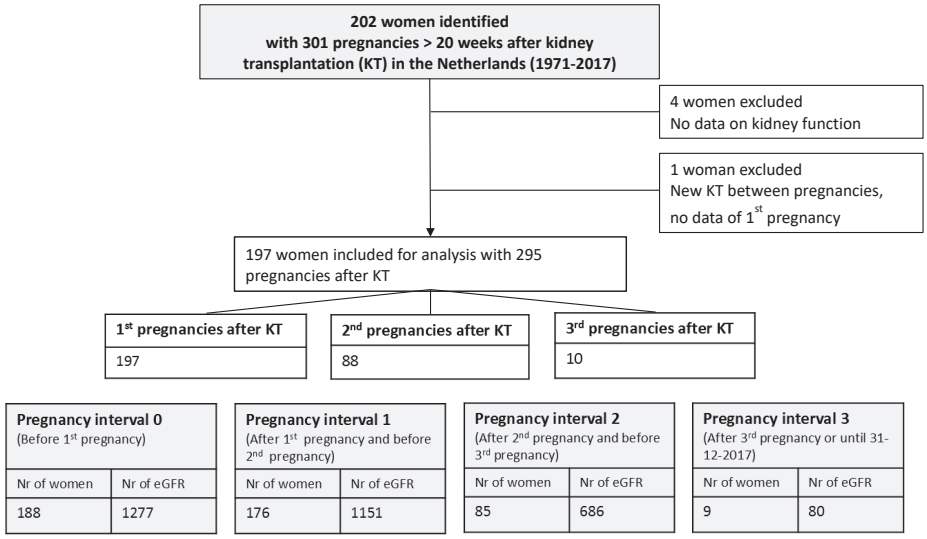


Figure 1: Flowchart *

*For missing subjects per interval see Appendix 1

Kidney Transplantation (KT)[1]	Pregnancy Interval 0	1st Pregnancy[3]	Pregnancy Interval 1	2nd Pregnancy	Pregnancy Interval 2	3rd Pregnancy	Pregnancy interval 3
	Annual eGFR[2] after KT before 1st conception + eGFR at 24, 18, 12, 6 months prior 1st conception and last eGFR before 1st conception		Annual eGFR after KT after 1st delivery and before 2nd conception or, if no 2nd pregnancy occurred, or until death or graft loss or until 31-12-2017 + eGFR at 24, 18, 12, 6 months prior 2nd conception and last SCr before 2nd conception		Annual eGFR after KT after 2nd delivery and before 3rd conception or, if no 3rd pregnancy occurred until death or graft loss, or until 31-12-2017 + eGFR at 24, 18, 12, 6 months prior 3rd conception and last SCr before 3rd conception		Annual eGFR after KT after 3rd delivery until death or graft loss or until 31-12-2017

Figure 2: Schematic overview of the study design

[1] Last KT before pregnancy

[2] eGFR calculated with CKD-EPI formula expressed in ml/min/1.73m^2

[3] 1st pregnancy means 1st pregnancy after KT, eGFR values during pregnancy, within 6 months after delivery and eGFR values before the age of 18 years were excluded from this analysis.

Statistical analysis

Data were analyzed using SPSS, version 25 (SPSS Inc) and Graph Pad prism version 8.4.1 (Graph Pad Software Inc). Two types of analyses were performed to examine the effect of pregnancy on kidney function after KT.

First, the effect of pregnancy on eGFR was explored by means of generalized estimating equation (GEE) analysis. GEE is an established method for multilevel analysis. GEE is a population average model, that captures average trajectories across the overall study population and estimates the marginal associations between the repeated outcome measures and the risk factors [27]. Therefore, GEE allows us to analyze the change in eGFR over time with varying numbers of observations per KT. The number of days after KT of each individual measurement was used as the within-subject level and as a continuous covariate (years after KT) in the model. In addition, eGFR measurements were divided in two to four 'pregnancy intervals', depending on the number of pregnancies (**Figure 2**). Analysis of the effect of pregnancy was adjusted for transplant vintage (years). Pregnancy interval was used as a categorical variable with pregnancy interval 0 as reference category.

Additionally, interaction was examined by adding the interaction term 'pregnancy interval*transplant vintage'. Because of the large number of within-subject levels, defined by time between eGFR measurement and KT, an exchangeable correlation matrix structure GEE analyses was used. This assumes a fixed correlation between eGFR measurements within the same subject.

Furthermore, a sub-GEE analysis was performed to identify other possible predictors for eGFR deterioration after KT. A dichotomous variable 'after first pregnancy' was created to discriminate eGFR's measured before or after first pregnancy. In this sub-analysis, the variable 'after first pregnancy' includes all eGFR measurements after first pregnancy (pregnancy interval 1), after second pregnancy (pregnancy interval 2) and after third pregnancy (pregnancy interval 3). For all prognostic variable's adjustments were made for transplant vintage. A directed acyclical graph was created to identify the most important potential confounders (Figure S1). Variables tested were; age at KT (years), year of KT, year of pregnancy, body mass index (BMI), primipara at first pregnancy after KT, living donor KT, pre-emptive KT, >1 KT before pregnancy, rejection before first pregnancy, transplant-to-conception interval in years, pre-pregnancy eGFR, pre-pregnancy hypertension and calcineurin inhibitor use. When a possible predictor turned out to be significant, the interaction term '[significant variable] * after first pregnancy' was added to the model. This additional analysis was performed to test if pregnancy amplifies the negative effect of the specific predictor on eGFR. Furthermore, for multivariate analysis all significant predictive variables were put together in the GEE model.

Secondly, we examined the association between possible predictors and DCGL after pregnancy. Kaplan Meijer and Cox proportional hazard regression analysis were performed to calculate hazard ratio (HR) and 95% confidence interval (CI). We tested the same possible predictors as used for the eGFR analysis. In the proportional hazard model, person time was counted from delivery date of their first pregnancy after KT until graft loss or December 31st, 2017. Censoring was applied in case of death or loss to follow-up.

RESULTS

Baseline characteristics (Table 1 & 2)

Table 1 shows baseline characteristics of the study participants (n=197), who had 295 pregnancies during follow-up. Characteristics of first pregnancies of these women are described in **Table 2**. Pregnancy outcomes were complicated by preterm birth (< 37 weeks) in more than 50% of the pregnancies, mean birthweight was 2281 (±853) gram. Of the 99 women who had hypertension before first pregnancy, we could retrieve hypertensive agents of 87 KT-recipients during the first trimester of their first pregnancy after transplantation. 70% had one antihypertensive agent, 29% had two antihypertensive agents and 1 woman had three antihypertensive agents. Gestational hypertension occurred in almost 46% of the women and preeclampsia in 31%. Almost half of the women had midterm hyperfiltration (SCr increase >15%). The differences in baseline characteristics of women transplanted before and after 1990 are highlighted in Table S1 & Table S2.

Table 1: Baseline Characteristics Women

	Total group N = 197	
	N (%)*/ Mean ±SD	Missing N (%)*
Follow-up time after first delivery (years)**	14 (18)	0
Total pregnancies	295	
1 pregnancy after KT	109 (55%)	
2 pregnancies after KT	78 (40%)	
3 pregnancies after KT	10 (5%)	
Cause of ESRD		18 (9%)
Glomerulonephritis	77 (39%)	
Diabetes mellitus	6 (3%)	
Auto-immune (SLE/vasculitis)	8 (4%)	
Tubulo-interstitial	29 (15%)	
Cystic kidney disease	8 (4%)	
Renal vascular disease (excl. vasculitis)	7 (4%)	
Urologic	7 (4%)	
Other congenital hereditary	23 (12%)	
Other multi cystic diseases	5 (3%)	
Other	22 (11%)	
Maternal death during follow-up	28 (14%)	0
Time between first delivery and death (years)**	14 (10)	
Age at KT (years)	25 (6.1)	0
Year of KT	1995 (11.6)	0
1971-1989	65 (33%)	
1990-1999	50 (25%)	
2000-2009	56 (28%)	
2010-2015	26 (13%)	
Living donor KT	83 (42%)	6 (3%)
Pre-emptive KT	36 (18%)	18 (9%)
> 1 KT before pregnancy	39 (20%)	5 (3%)
Rejection before pregnancy	68 (35%)	46 (23%)
Graft loss during pregnancy	1 (0.5%)	0
Graft loss after first pregnancy	42 (24%)	25 (13%)
Time between first pregnancy and graft loss (years)**	6 (7)	0
Time between KT and graft loss (years)**	12 (7)	0

KT: kidney transplantation (last KT before pregnancy), eGFR: estimated Glomerular Filtration Rate, ESRD: end stage renal disease, MAP: mean arterial pressure, CNI: calcineurine inhibitors, BMI: body mass index, SCr: serum creatinine, SD: standard deviation * Due to rounding it can be possible that percentages not reach 100%, **Me

Table 2: Characteristics of all 1st pregnancies (n=197)

	Total group N = 197	
	N (%)*/ Mean ±SD	Missing N (%)*
KT to conception interval (year) **	4 (6)	8 (4%)
0- 2 year	29 (15%)	
2 – 4 year	78 (41%)	
5 – 9 years	49 (25%)	
10 - 24 years	33 (17%)	
Pre-pregnancy eGFR	62 (±21)	7 (4%)
eGFR < 45 ml/min/1.73m²	34 (17%)	
eGFR < 30 ml/min/ 1.73m²	8 (4%)	
Pre-pregnancy MAP	95 (±11)	38 (19%)
Pre-pregnancy hypertension	99 (50%)	24 (12%)
CNI before first pregnancy	97 (49%)	8 (4%)
Year of pregnancy	2001 (±10.9)	0
1979-1989	37 (19%)	
1990-1999	44 (22%)	
2000-2009	54 (27%)	
2010-2017	62 (32%)	
Pre-pregnancy BMI	25 (±4)	70 (36%)
Primipara at first pregnancy after KT	154 (78%)	5 (3%)
Pregnancy outcomes		
Preterm < 37 weeks	102 (52%)	13 (7%)
Preterm < 34 weeks	50 (25%)	
Birthweight (gram)	2281 (±853)	13 (7%)
Low birthweight (<2500 gram)	103 (52%)	
Very low birthweight (<1500 gram)	30 (15%)	
Gestational hypertension	90 (46%)	37 (19%)
Severe hypertension ***	30 (15%)	56 (28%)
Preeclampsia	60 (31%)	32 (16%)
% Scr decrease during pregnancy	17 (±10)	45 (23%)
> 15% Scr decrease during pregnancy	90 (46%)	

KT: kidney transplantation (last KT before pregnancy), eGFR: estimated Glomerular Filtration Rate, ESRD: end stage renal disease, MAP: mean arterial pressure, CNI: calcineurine inhibitors, BMI: body mass index, SCr: serum creatinine, SD: standard deviation * Due to rounding it can be possible that percentages not reach 100%, **Median (IQR), *** RR systolic ≥160 mmHg and/ or diastolic ≥ 100 mmHg

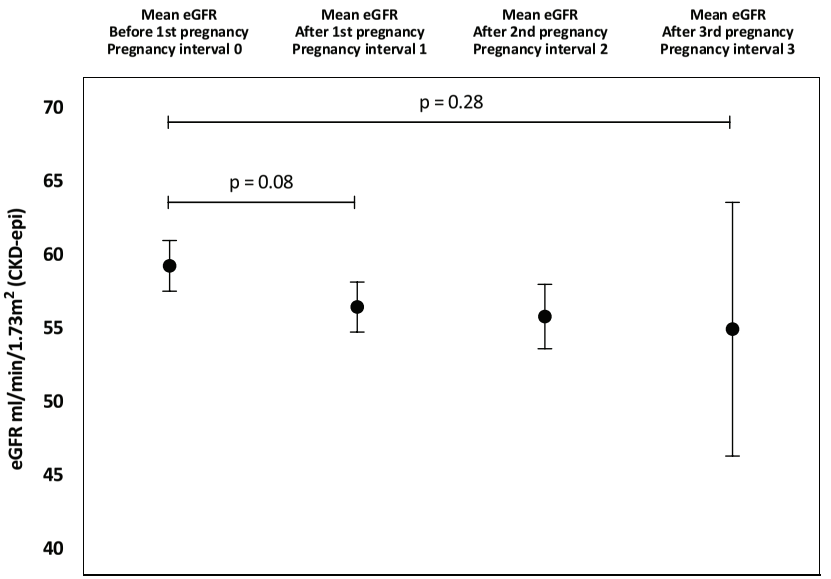
Change of mean eGFR before and after pregnancy (Figure 3 & 4)

Of the 197 KT-recipients with at least 1 pregnancy, of 9 women (5%) no eGFR was available before pregnancy (pregnancy interval 0), mostly because they got pregnant within 6 months after KT. Of 17 KT-recipients (9%) no eGFR was available of pregnancy interval 1, main reason because their second pregnancy soon followed and no eGFR of pregnancy interval 1 could be included. Nevertheless, the follow-up of these women were continued after second pregnancy in pregnancy interval 2, and if a 3rd pregnancy occurred also in pregnancy interval 3. Specified reasons for missing values per subject are described in Table S3.

In our study population of 197 KT-recipients the overall effect of transplant vintage on eGFR slope was -0.58 ml/min/1.73m² per year (SEM 0.13; 95% CI -0.84 - -0.31; *p* = <0.001). Overall mean eGFR after first, second and third pregnancy was not significantly worse than pre-pregnancy (*p* = 0.28). Adjusted mean eGFR decline in pregnancy interval 1 was -2.80 ml/min/1.73m² (SEM 1.59; 95% CI -5.92 – 0.33; p = 0.08) over a median of 2.57 years (IQR 7.06). During pregnancy interval 2 mean eGFR decline was -3.45 ml/min/1.73m², (SEM 2.24; 95% CI -7.84 – 0.94; p= 0.12) over a median of 5.02 years (IQR 11.87). And during pregnancy interval 3 mean eGFR decline was -4.31 ml/min1.73m² (SEM 8.89; 95% CI -21.73 – 13.11; p = 0.63) over a median of 6.52 years (IQR 18.80). Adjusted mean eGFR's per pregnancy interval are illustrated in **Figure 3**. Pregnancy interval 3 (i.e. eGFR measurements after 3rd pregnancy after KT) had a wide confidence interval due to a small number of KT-recipients included. As expected, time between the first and last eGFR measurements was longer after second and third pregnancies as shown in **Figure 3**. The same analysis was also performed with KT-recipients that only had 1 pregnancy after KT. In this analysis mean eGFR after pregnancy was significant lower (p = 0.02) (Figure S2).

To test if pregnancy causes a faster decline of eGFR, the interaction term pregnancy interval*transplant vintage was added to the model. The interaction term pregnancy interval*transplant vintage was not significant for pregnancy interval 1 (B = -0.29, *p* = 0.29, pregnancy interval 2 (B = -0.55, *p* =0.08) and pregnancy interval 3 (B = -0.46, *p* = 0.39). No additional effect of pregnancy on eGFR slope was observed.

Figure 4 illustrates the estimated marginal means per year of eGFR before and after first pregnancy adjusted for transplant vintage. To calculate the marginal means per year before and after first pregnancy an additional GEE model was constructed. For this GEE model a dichotomous variable 'after first pregnancy' was created (i.e. before or after first pregnancy). 'After first pregnancy' implies all eGFR measurements after first, second and third pregnancy. The variables 'after first pregnancy' and 'Years after first pregnancy' (after rounding visit dates into whole years) were added to the model as categorical factors.



Total nr. of eGFR	1277	1151	686	80
Women included	188	176	85	9
Nr. of eGFR per woman*	6 (5)	5 (6)	6 (9)	7 (14)
Yrs. after KT first eGFR – last eGFR*	1.00 (0.66) -4.07 (5.76)	5.72 (5.51) -10.39 (10.67)	9.64 (6.57)-16.06 (15.99)	13.11 (5.52)–21.92 (11.05)
Yrs. between first and last eGFR*	2.28 (3.64)	2.57 (7.06)	5.02 (11.87)	6.52 (18.80)
eGFR decline per pregnancy interval (compared to interval 0)**	Reference***	-2.80 ml/min/1.73m² (1.59) (*p* = 0.08)	-3.45 ml/min/1.73m² (2.24) (*p* = 0.12)	-4.31 ml/min/1.73m² (8.89) (*p* = 0.63)

Figure 3: Adjusted man eGFR before and after pregnancies after kidney transplantation (GEE) (n=197)

*Median (IQR), **mean (SEM), and ***annual eGFR decline after KT in this population: mean 0.58 mL/min/1.73 m2 (SEM 0.13). In this model, "years after KT" was used as a continuous covariate and "pregnancy interval" as a categorical factor. Error bars illustrate SD. eGFRs during pregnancy and within 6 mo after delivery were excluded. CKD-epi, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; GEE, generalized estimated equations—a multilevel method; KT, kidney transplantation (last KT before pregnancy); SEM, standard error of the mean; subject level, subject ID; within-subject level, days after KT.

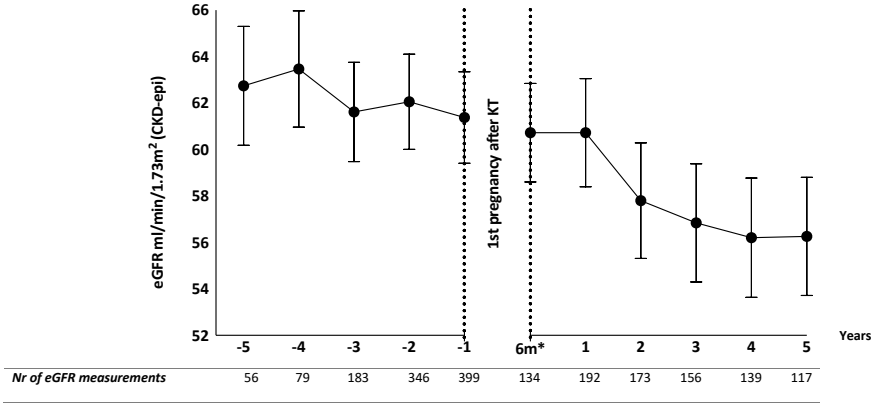


Figure 4: Adjusted mean eGFR before and after first pregnancy after KT (GEE).

In this model, "years after KT" was used as a continuous covariate, "pregnancy interval" and "years after pregnancy" as categorical factors. Error bars illustrate SD. eGFRs during pregnancy and within 6 mo after delivery were excluded. *6 mo after first delivery after KT. For this analysis, all eGFR measurements after first pregnancy were included, also eGFR measurements after second (pregnancy interval 2) and third pregnancies (pregnancy interval 3). CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; GEE, generalized estimated equations—a multilevel method; KT, kidney transplantation; subject level, subject ID; within-subject level, days after KT

Other predictors that effect eGFR after KT (Table 3)

To determine which other predictors might have an effect on eGFR after KT, we performed a GEE analysis with possible predictors of deterioration of eGFR. For this analysis all eGFR measurements after first pregnancy were included, also eGFR measurements after second (pregnancy interval 2) and third pregnancy (pregnancy interval 3). All variables were analyzed with adjustment for transplant vintage.

First, time-related variables were tested. Women who were transplanted and pregnant before 1990 had significantly better post-transplant eGFR, than women who were transplanted and pregnant more recently ($p < 0.01$). Also, KT at a younger age was related to better eGFR after KT. This effect was no longer significant after exclusion of women who received a transplant before the age of 18 ($p = 0.11$). Women conceiving with a transplant-to-conception interval of more than 10 years had a higher post-transplant eGFR. However, when excluding the group with a transplant-to-conception interval longer than 10 years, no significant effect of transplant-to-conception interval on eGFR was observed. Adjusted post-transplant eGFR was higher in women who had not been pregnant before KT. Rejection, pre-pregnancy hypertension, mean arterial pressure (MAP), and calcineurin inhibitor (CNI) use had a significant negative effect on post-transplant eGFR.

After identifying these predictors for worse eGFR after KT, the additive effect of pregnancy on eGFR was tested. Therefore the interaction term '[significant variable]*after first pregnancy' was added to the univariate model. This interaction term was only significant for pre-pregnancy eGFR (B -0.120, SEM 0.06, p = 0.048), concluding that lower pre-pregnancy eGFR causes worse eGFR after pregnancy. There was no interaction with other variables affecting post-transplant eGFR. Therefore, pregnancy seems not to amplify the negative effect of these predictors on eGFR decline after KT.

Finally, when all significant variables were put together (except year of KT and year of first delivery after KT) in a multivariate GEE model, transplant vintage, rejection before first pregnancy, pre-pregnancy eGFR, and transplant-to-conception interval were independent risk factors for accelerated eGFR decline after KT (**Table 4**).

Additionally, univariate analysis of the effect of pregnancy outcomes on eGFR after pregnancy was performed (**Table 5**). For this analysis eGFR measurements after second and third pregnancy were excluded. This analysis was also adjusted for transplant vintage and pregnancy interval. Midterm hyperfiltration was related with better eGFR after pregnancy (p = 0.04), while low birthweight tended to be related with worse eGFR after first pregnancy (p = 0.06). When these outcomes were added to the multivariate model, none of them were identified as independent predictors for worse eGFR after pregnancy (Table S4).

Table 3: Effect of predictors on eGFR slope after KT (univariate analysis, GEE)

	B coëfficiënt	Standard error of the mean (SEM)	p-value**
Glomerulonephritis	1.01	3.13	0.75
Age at KT (year)	**-0.61**	**0.23**	**0.01**
Age at 1st delivery (year)	-0.01	0.29	0.98
Year of KT ≥ 1990	**-10.90**	**3.16**	**<0.01**
BMI before 1st pregnancy	0.15	0.52	0.77
Primipara at 1st pregnancy after KT	**7.94**	**3.75**	**0.03**
Living KT	-4.35	2.94	0.20
Pre-emptive KT	-0.82	3.59	0.98
> 1 KT before pregnancy	2.44	3.27	0.45
Rejection before 1st pregnancy	**-7.01**	**4.09**	0.046
KT to 1st conception interval (year)	**1.15**	**0.31**	**<0.01**
< 2 year*	Ref.	--	-
2-4 year	5.33	3.98	0.18
5-9j year	7.95	4.93	0.11

Table 3: Effect of predictors on eGFR slope after KT (univariate analysis, GEE) *Continued*

	B coëfficiënt	Standard error of the mean (SEM)	p-value**
10-24 year	**16.77**	**4.92**	**<0.01**
Pre-pregnancy eGFR (1st pregnancy)	**0.82**	**0.05**	**<0.01**
Pre-preg. eGFR <45ml/min/1.73m² (1st pregnancy)	**-27.94**	**2.28**	**<0.01**
Pre-pregnancy MAP (1st pregnancy)	**-0.43**	**0.15**	**<0.01**
Pre-pregnancy hypertension (1st pregnancy)	**-9.10**	**3.01**	**<0.01**
CNI before 1st pregnancy	**-9.49**	**2.90**	**<0.01**

GEE: generalized estimated equations; a multilevel method. Subject level: subject ID, Within-subject level: days after KT. In the model, transplant vintage (years) was used as a continuous covariate. All variables above were added one by one to the model. KT: kidney transplantation (last KT before pregnancy), BMI: body mass index, eGFR: estimated Glomerular Filtration Rate, CNI: calcine urine inhibitors, For this analysis a dichotomous variable 'After first pregnancy' was created (before or after pregnancy). After pregnancy means all eGFR measurements after 1st pregnancy (pregnancy interval 1), after 2nd pregnancy (pregnancy interval 2) and after 3rd pregnancy (pregnancy interval 3). eGFRs during pregnancy and within 6 months after delivery were excluded.

* Used as reference category

** For all significant variables the interaction with 'after first pregnancy' was added to the model, only pre-pregnancy eGFR*after first pregnancy was significant (B -0,120, SEM 0.06, P 0.048), in all the other variables the interaction term was not significant.

Table 4: Effect of predictors on eGFR slope after KT (multivariate analysis, GEE)

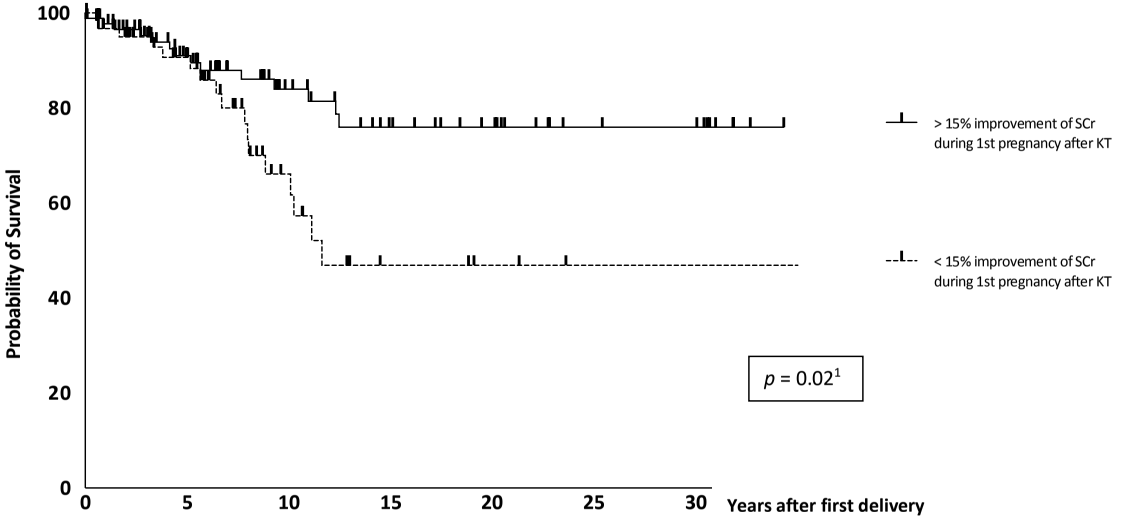
	B coëfficiënt	Standard error of the mean (SEM)	p-value
After first pregnancy	**-2.90**	**1.83**	**0.11**
Year of KT ≥ 1990	**-1.54**	**1.86**	**0.41**
Transplant vintage (years)	**-0.72**	**0.17**	**<0.01**
Age at KT	0.16	0.20	0.41
Primipara	2.30	2.09	0.27
Rejection before 1st pregnancy	**-4.12**	**1.59**	**0.01**
KT to 1st conception interval (years)	**0.84**	**0.26**	**<0.01**
Pre-pregnancy eGFR (1st pregnancy)	**0.81**	**0.04**	**<0.01**
Pre-pregnancy hypertension (1st pregnancy)	-1.20	1.94	0.54
CNI before 1st pregnancy	0.47	1.54	0.76

For this analysis a dichotomous variable 'After first pregnancy' was created (before or after pregnancy). After pregnancy means all eGFR measurements after 1st pregnancy (pregnancy interval 1), after 2nd pregnancy (pregnancy interval 2) and after 3rd pregnancy (pregnancy interval 3). eGFRs during pregnancy and within 6 months after delivery were excluded.
eGFR: estimated Glomerular Filtration Rate, CNI: calcineurin inhibitor, GEE: generalized estimated equations, KT: kidney transplantation

Table 5: Effect of 1st pregnancy outcomes after KT on eGFR slope (univariate analysis, GEE)

	B coëfficiënt	Standard error of the mean (SEM)	p-value**
Preterm birth < 37 weeks	-4.74	2.65	0.74
Low birthweight <2500 gram	**-5.12**	**2.75**	**0.06**
Very low birthweight <1500 gram	-2.04	4.09	0.62
Gestational hypertension	**3.95**	**2.84**	**0.16**
Severe hypertension	-4.31	3.75	0.25
Preeclampsia	-0.97	2.72	0.72
> 15% SCr decrease during pregnancy	**5.87**	**2.81**	**0.04**

GEE: generalized estimated equations; a multilevel method. Subject level: subject ID, Within-subject level: days after KT. In the model, transplant vintage (years) was used as a continuous covariate. All variables above were added one by one to the model. KT: kidney transplantation (last KT before pregnancy), SCr: serum creatinine. * RR systolic ≥160 mmHg and/or diastolic ≥ 100 mmHg. eGFRs during pregnancy and within 6 months after delivery were excluded. For this analysis eGFR measurements after 2nd and 3rd pregnancy were excluded. ** For all significant variables the interaction with pregnancy interval was added to the model, in none of the cases the interaction term was significant



SCr[2] improvement during 1st pregnancy	Nrs. at risk							
> 15 % SCr	90	62	36	25	19	11	10	1
< 15% SCr	63	40	16	7	5	3	3	3

Figure 5: Graft survival after first delivery after kidney transplantation (censored for death)

[1] mulivariate Cox regression: hazard ratio, 2.31; 95% confidence interval, 1.13-4.72.

[2] SCr: Serum Creatin

Kaplan Meier and Cox regression (Figure 5)

Kaplan Meier and Cox regression analysis were performed to evaluate graft survival and risk factors. Overall, approximately 10% of the women lost their graft within 5 years after delivery and 20% within 10 years after first delivery. Cox regression analysis was performed to identify risk factors for DCGL. Women with a pre-pregnancy eGFR <45 ml/min/1.73m² had shorter graft survival (HR 0.48; 95% CI 0.24-0.94; p = 0.03). No difference in DCGL was observed between women with eGFR values between 45 and 60 ml/min/1.73m² and eGFR values >60 ml/min/1.73m². Furthermore, transplant-to-conception interval had no significant effect on DCGL (HR 0.94; 95% CI 0.86-1.02; p = 0.14) **Figure 5** shows that women with midterm hyperfiltration during their first pregnancy after KT had better graft survival than women without midterm hyperfiltration (HR 2.31; 95%CI 1.13-4.72; p = 0.02). Pre-pregnancy MAP and pre-pregnancy hypertension were not related with DCGL. However, low birthweight was related to an increased risk of DCGL.

DISCUSSION

In this study, we report on longitudinal data of kidney function after pregnancy in women following KT. To our knowledge, no previous reports have been published on eGFR slope after pregnancy in KT-recipients with proper multilevel analysis, which allows women to be their own control group. For our analysis, we used a large, unique and unselected retrospective dataset from the nation-wide Dutch PARTOUT Study. We identified four important findings. First in general, pregnancies after KT have no significant effect on eGFR and pregnancy did not accelerate eGFR slope. Secondly, pregnancy does not amplify the negative effect of significant univariate predictors of worse eGFR (e.g. rejection, hypertension, CNI use) after KT. Thirdly, multivariate GEE analysis showed that transplant vintage, rejection before first pregnancy, pre-pregnancy eGFR and transplant-to-conception interval are predictors for worse eGFR after KT and not pregnancy itself. Finally, eGFR and graft survival after first delivery were significant better for women with midterm hyperfiltration (>15% SCr decrease) during first pregnancy.

We found that eGFR decline after first pregnancy was not statistically significant (p=0.08). The almost significant decline in eGFR after first pregnancy can be explained by the fact that most women in this subgroup only had one pregnancy after KT. It is likely that, if complications occurred during this pregnancy or if their kidney function decreased, these women decided not to become pregnant again.

Furthermore, 10 KT-recipients were pregnant again very soon after their first delivery therefore no eGFR's of these KT-recipients could be included in pregnancy interval 1. Although pregnancy causes a non-significant slight drop in adjusted mean eGFR of approximately 3 ml/min/1.73m^2, it is questionable if such a slight drop is clinically significant. These findings are in line with our previous meta-analysis [28]. Furthermore, it is reassuring that pregnancy does not seem to have an effect on eGFR after second and third pregnancies, of course in a selected "best KT-recipients" group, pregnancy did not have any additional effect on eGFR slope.

Pre-pregnancy eGFR was a strong predictor for better eGFR after pregnancy. Although previous studies are hardly comparable to our study, due to heterogeneity in SCr cut-off values in these studies, this result is in line with the findings of most of these studies. [9,20,29-35]. However, three studies did not find a negative effect of pre-pregnancy SCr on long-term graft function [31,36,37]. This discrepancy might be due to the fact that these studies were underpowered. Moreover, their follow-up after pregnancy consisted of a one-year SCr measurement, instead of the long-term follow-up that took place in our study [28]. Hypertension is a known risk factor for eGFR decline in the CKD population[38]. In this study it was only a significant risk factor in the univariate analysis.

The relationship between transplant-to-conception interval and graft function after pregnancy was reported earlier by five individual studies. These studies report on different periods of transplant to conception interval (as a continuous variable, transplant-to-conception interval < 1 yr, transplant-to-conception interval <2 yr, transplant-to-conception interval >5 yr) [7,8,33,34,39]. No negative relationship was found between SCr one year after pregnancy and transplant-to-conception interval [8,34,39]. We also found no effect of transplant-to-conception interval on mean eGFR for women with a transplant-to-conception interval <10 years. However, a transplant-to-conception interval > 10 year resulted in significantly better mean eGFR than women who got pregnant at shorter times after KT. This can be due to the fact that women who were transplanted at childhood selectively received a donor kidney of very good quality. And only good kidneys have long enough graft survival until fertile age is reached. After exclusion of KT-recipients transplanted in childhood the relation between age and time of KT and mean eGFR after pregnancy was no longer significant. No relationship with DCGL and transplant-to-conception interval was found in our study, this in contrast with the study by Rose [40]. Therefore, outcomes of our study give no grounds to change the 'timing of pregnancy' advice of the American Society of Transplantation guidelines of > 1 year after KT [41]

Surprisingly, known predictors for better graft survival in the general KT population, such as preemptive KT and KT with a living kidney, were not associated with

better eGFR or better graft survival after pregnancy [42,43]. This may have been due to the fact that in the past, KT with a living kidney was not the standard of care and most of these women were transplanted with a deceased donor. Moreover, only women with excellent kidney function were 'allowed' to get pregnant, so the best of the deceased donor KT's is over-represented in our dataset. This era effect was also described in an earlier study [10].

Both mean eGFR and graft survival after pregnancy was better in the group with more than 15% decrease in SCr during first pregnancy. This shows that the functional reserve capacity of the KT can be an important sign of the quality of the graft. As expected, graft survival was better when pre-pregnancy eGFR was better according to a study performed earlier in the general KT population [44].

This study has several limitations. One limitation is that the study is retrospective; therefore, not all data could be obtained and residual confounding cannot be excluded. Unfortunately, data on proteinuria and immune status such as HLA-antibodies and HLA mismatches were insufficient for analysis [45]. For measurement of kidney function during pregnancy the golden standard is 24hours urine creatinine clearance, unfortunately we did not have those measurements available[46]. Although being retrospective in nature, our study allowed proper analyses of eGFR in an unselected, large cohort of KT-recipients with pregnancy. This is the first study that compares eGFR's pre-pregnancy and post-pregnancy by multi-level analysis, correcting for missing values and correcting for time in the model. Also, the nation-wide composition of our cohort provides strong external validity.

In conclusion, to the best of our knowledge, this is the largest study analyzing the effect of pregnancy in KT-recipients on eGFR slope to date. The outcomes of our study demonstrate that pregnancy causes a small and non-significant decline in adjusted mean eGFR after first pregnancy, but does not accelerate eGFR slope after first or subsequent pregnancies. Furthermore, pregnancy does not amplify the negative effect of known risk factors on eGFR after KT. Midterm hyperfiltration might be a marker for favorable graft outcomes after pregnancy. The absence of midterm hyperfiltration as a marker of renal reserve might be considered as a risk factor for long-term graft loss in addition to traditional risk factors.

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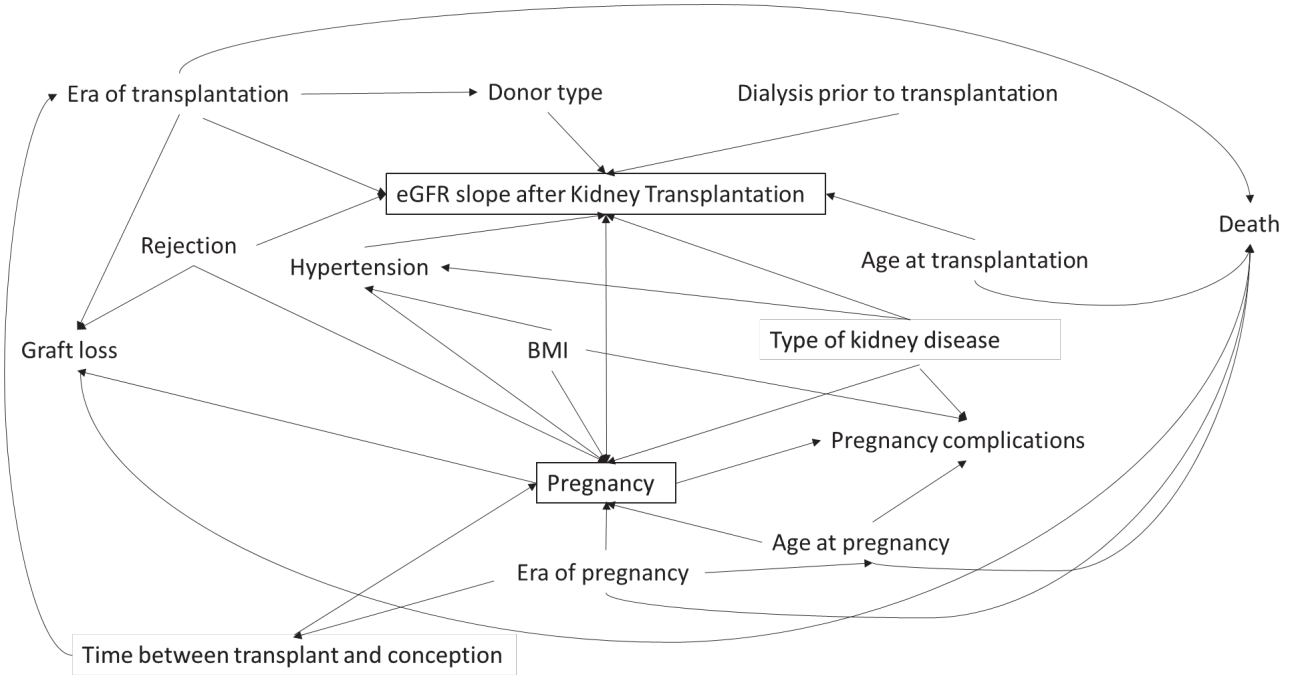
REFERENCES

1. Moritz MJ CS, Coscia LA, et al. Transplant Pregnancy Registry International (TPR). *2017 annual report.* Philadelphia PA: Gift of Life Institute; 2018:0-21.
2. McKay DB, Josephson MA. Reproduction and Transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. *American Journal of Transplantation.* 2005;5(7): 1592-1599.
3. First MR, Combs CA, Weiskittel P, Miodovnik M. Lack of effect of pregnancy on renal allograft survival or function. *Transplantation.* 1995;59(4): 472-476.
4. Sturgiss SN, Davison JM. Effect of pregnancy on the long-term function of renal allografts: an update. *Am J Kidney Dis.* 1995;26(1): 54-56.
5. Fischer T, Neumayer HH, Fischer R, et al. Effect of pregnancy on long-term kidney function in renal transplant recipients treated with cyclosporine and with azathioprine. *Am J Transplant.* 2005;5(11): 2732-2739.
6. Pour-Reza-Gholi F, Nafar M, Farrokhi F, et al. Pregnancy in kidney transplant recipients. *Transplant Proc.* 2005;37(7): 3090-3092.
7. Rahamimov R, Ben-Haroush A, Wittenberg C, et al. Pregnancy in renal transplant recipients: long-term effect on patient and graft survival. A single-center experience. *Transplantation.* 2006;81(5): 660-664.
8. Kashanizadeh N, Nemati E, Sharifi-Bonab M, et al. Impact of pregnancy on the outcome of kidney transplantation. *Transplant Proc.* 2007;39(4): 1136-1138.
9. Kim HW, Seok HJ, Kim TH, Han DJ, Yang WS, Park SK. The experience of pregnancy after renal transplantation: pregnancies even within postoperative 1 year may be tolerable. *Transplantation.* 2008;85(10): 1412-1419.
10. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J Am Soc Nephrol.* 2009;20(11): 2433-2440.
11. Stoumpos S, McNeill SH, Gorrie M, et al. Obstetric and long-term kidney outcomes in renal transplant recipients: a 40-yr single-center study. *Clin Transplant.* 2016;30(6): 673-681.
12. Svetitsky S, Baruch R, Schwartz IF, et al. Long-Term Effects of Pregnancy on Renal Graft Function in Women After Kidney Transplantation Compared With Matched Controls. *Transplant Proc.* 2018;50(5): 1461-1465.
13. Lopes van Balen VA, van Gansewinkel TAG, de Haas S, et al. Maternal kidney function during pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2019;54(3): 297-307.
14. Paauw ND, van der Graaf AM, Bozoglan R, et al. Kidney Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study. *Am J Kidney Dis.* 2018;71(5): 619-626.
15. Park S, Lee SM, Park JS, et al. Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of Gestational Hyperfiltration. *Clin J Am Soc Nephrol.* 2017;12(7): 1048-1056.
16. Bramham K, Nelson-Piercy C, Gao H, et al. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol.* 2013;8(2): 290-298.
17. van Buren MC, Schellekens A, Groenhof TKJ, et al. Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis. *Transplantation.* 2020;104(8): 1675-1685.

18. Basaran O, Emiroglu R, Secme S, Moray G, Haberal M. Pregnancy and renal transplantation. *Transplant Proc.* 2004;36(1): 122-124.
19. Little MA, Abraham KA, Kavanagh J, Connolly G, Byrne P, Walshe JJ. Pregnancy in Irish renal transplant recipients in the cyclosporine era. *Ir J Med Sci.* 2000;169(1): 19-21.
20. Thompson BC KE, Tuck SM, Fernando ON, Sweny P. Pregnancy in renal transplant recipients: the Royal Free Hospital experience. *Q J Med.* 2003;96: 837-844.
21. Open Clinica, version 3.1. Copyright © OpenClinica LLC and collaborators, Waltham, MA, USA, www.OpenClinica.com. 2017. Accessed 31-12-2017.
22. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC, Guideline C. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. *BMJ.* 2019;366: l5119.
23. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol.* 1988;158(4): 892-898.
24. Lopes van Balen VA, Spaan JJ, Ghossein C, van Kuijk SM, Spaanderman ME, Peeters LL. Early pregnancy circulatory adaptation and recurrent hypertensive disease: an explorative study. *Reprod Sci.* 2013;20(9): 1069-1074.
25. Sturgiss SN, Dunlop W, Davison JM. Renal haemodynamics and tubular function in human pregnancy. *Baillieres Clin Obstet Gynaecol.* 1994;8(2): 209-234.
26. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis.* 2010;55(4): 622-627.
27. Shou H, Hsu JY, Xie D, et al. Analytic Considerations for Repeated Measures of eGFR in Cohort Studies of CKD. *Clinical journal of the American Society of Nephrology : CJASN.* 2017;12(8): 1357-1365.
28. van Buren MC, Schellekens A, Groenhof TKJ, et al. Long term graft survival and graft function following pregnancy in kidney transplant recipients: a systematic review and meta-analysis. *Transplantation.* 2019.
29. Queipo-Zaragoza JA, Vera-Donoso CD, Soldevila A, Sanchez-Plumed J, Broseta-Rico E, Jimenez-Cruz JF. Impact of pregnancy on kidney transplant. *Transplant Proc.* 2003;35(2): 866-867.
30. Kato M, Hattori R, Kinukawa T, Kamihira O, Yamada S, Gotoh M. Correlation between treated hypertension in prepregnancy and transplanted kidney function deterioration during pregnancy even if within pregnancy permission criteria. *Transplant Proc.* 2012;44(3): 635-637.
31. Rocha A, Cardoso A, Malheiro J, et al. Pregnancy after kidney transplantation: graft, mother, and newborn complications. *Transplant Proc.* 2013;45(3): 1088-1091.
32. O'Reilly B, Compton F, Ogg C, Pattison J, Maxwell D. Renal function following pregnancy in renal transplant recipients. *J Obstet Gynaecol.* 2001;21(1): 12-16.
33. Keitel E, Bruno RM, Duarte M, et al. Pregnancy outcome after renal transplantation. *Transplantation Proceedings.* 2004;36(4): 870-871.
34. Aivazoglou L, Sass N, Silva HT, Jr., Sato JL, Medina-Pestana JO, De Oliveira LG. Pregnancy after renal transplantation: an evaluation of the graft function. *Eur J Obstet Gynecol Reprod Biol.* 2011;155(2): 129-131.
35. Alfi AY, Al-essawy MA, Al-Iakany M, Somro A, Khan F, Ahmed S. Successful pregnancies post renal transplantation. *Saudi J Kidney Dis Transpl.* 2008;19(5): 746-750.
36. Hooi LS, Rozina G, Shaariah MY, et al. Pregnancy in patients with renal transplants in Malaysia. *Med J Malaysia.* 2003;58(1): 27-36.

37. Vannevel V, Claes K, Baud D, et al. Preeclampsia and Long-term Renal Function in Women Who Underwent Kidney Transplantation. *Obstet Gynecol.* 2018;131(1): 57-62.
38. Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: Core Curriculum 2019. *American Journal of Kidney Diseases.* 2019;74(1): 120-131.
39. Chittka D, Hutchinson JA. Pregnancy After Renal Transplantation. *Transplantation.* 2017;101(4): 675-678.
40. Rose C, Gill J, Zalunardo N, Johnston O, Mehrotra A, Gill JS. Timing of Pregnancy After Kidney Transplantation and Risk of Allograft Failure. *Am J Transplant.* 2016;16(8): 2360-2367.
41. McKay DB, Josephson MA, Armenti VT, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant.* 2005;5(7): 1592-1599.
42. Arze Aimaretti L, Arze S. Preemptive Renal Transplantation-The Best Treatment Option for Terminal Chronic Renal Failure. *Transplant Proc.* 2016;48(2): 609-611.
43. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High Survival Rates of Kidney Transplants from Spousal and Living Unrelated Donors. *New England Journal of Medicine.* 1995;333(6): 333-336.
44. Kasiske BL, Israni AK, Snyder JJ, Skeans MA, Patient Outcomes in Renal Transplantation I. The relationship between kidney function and long-term graft survival after kidney transplant. *Am J Kidney Dis.* 2011;57(3): 466-475.
45. Zhang R. Donor-Specific Antibodies in Kidney Transplant Recipients. *Clin J Am Soc Nephrol.* 2018;13(1): 182-192.
46. Ahmed SB, Bentley-Lewis R, Hollenberg NK, Graves SW, Seely EW. A comparison of prediction equations for estimating glomerular filtration rate in pregnancy. *Hypertens Pregnancy.* 2009;28(3): 243-255.

Appendix 1: Directed Acyclic Graph



Appendix 2A: Baseline Characteristics Women transplanted before and after 1990

	Total group N = 197		Transplanted ≥ 1990 N = 132		Transplanted < 199 N = 65	
	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*
Follow-up time after first delivery (years)**	14 (18)	0	9 (10)	0	28 (9)	0
Total pregnancies	295		188		107	
1 pregnancy after KT	109 (55%)		79 (60%)		30 (46%)	
2 pregnancies after KT	78 (40%)		50 (38%)		28 (43%)	
3 pregnancies after KT	10 (5%)		3 (2%)		7 (11%)	
Cause of ESRD		18 (9%)		13 (10%)		
Glomerulonephritis	77 (39%)		48 (36%)		29 (45%)	
Diabetes mellitus	6 (3%)					
Auto-immune (SLE/vasculitis)	8 (4%)					
Tubulo-interstitial	29 (15%)					
Cystic kidney disease	8 (4%)					
Renal vascular disease (excl. vasculitis)	7 (4%)					
Urologic	7 (4%)					
Other congenital hereditary	23 (12%)					
Other multi cystic diseases	5 (3%)					
Other	22 (11%)					
Maternal death during follow-up	28 (14%)	0	8 (6%)	0	20 (31%)	0
Time between first delivery and death (years)**	14 (10)		9 (5)		16 (15)	
Age at KT (years)	25 (6)	0	27 (8)	0	24 (9)	
Year of KT	1995 (12)	0	2003 (13)	0	1982 (9)	0

Appendix 2A: Baseline Characteristics Women transplanted before and after 1990 *Continued*

	Total group N = 197		**Transplanted ≥ 1990 N = 132**		**Transplanted < 199 N = 65**	
	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*
1971-1989	65 (33%)					
1990-1999	50 (25%)					
2000-2009	56 (28%)					
2010-2015	26 (13%)					
Living donor KT	83 (42%)	6 (3%)	78 (59%)	2 (2%)	5 (8%)	4(6%)
Pre-emptive KT	36 (18%)	18 (9%)	32 (24%)	12 (9%)	4 (6%)	6 (9%)
> 1 KT before pregnancy	39 (20%)	5 (3%)	23 (17%)	3 (2%)	16 (25%)	2 (3%)
Rejection before pregnancy	68 (35%)	46 (23%)	37 (28%)	30 (23%)	30 (46%)	16 (25%)
Graft loss during pregnancy	1 (0.5%)	0	1 (0.5%)	0		
Graft loss after first pregnancy	42 (24%)	25 (13%)	26 (20%)	13 (10%)	16 (25%)	12 (19%
Time between first pregnancy and graft loss (years)**	6 (7)	0	6 (5)	0	8 (8)	0
Time between KT and graft loss (years)**	12 (7)	0	11 (7)	0	13 (7)	0

KT: kidney transplantation (last KT before pregnancy), eGFR: estimated Glomerular Filtration Rate, ESRD: end stage renal disease, MAP: mean arterial pressure, CNI: calcineurine inhibitors, BMI: body mass index, SCr: serum creatinine, SD: standard deviation * Due to rounding it can be possible that percentages not reach 100%, **Median (IQR)

Appendix 2B: Characteristics of all 1st pregnancies (n=197) before and after 1990

	Total group N = 197		Transplanted ≥ 1990 = 132		Transplanted < 1990 N = 65	
	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*
KT to conception interval (year) **	4 (6)	8 (4%)	4 (5)	3 (2%)	5 (6)	5 (8%)
0- 2 year	29 (15%)					
2 – 4 year	78 (41%)					
5 – 9 years	49 (25%)					
10 - 24 years	33 (17%)					
Pre-pregnancy eGFR	62 (±21)	7 (4%)	58 (±19)	3 (2%)	71 (±24)	4 (6%)
eGFR < 45 ml/min/1.73m²	34 (17%)		25 (19%)		9 (14%)	
eGFR < 30 ml/min/ 1.73m²	8 (4%)		4 (3%)		4 (6%)	
Pre-pregnancy MAP	95 (±10)	30 (15%)	94 (±10)	15 (11%)	97 (±12)	15 (23%)
Pre-pregnancy hypertension	99 (50%)	24 (12%)	71 (54%)	12 (9%)	28 (43%)	12 (19%)
CNI before first pregnancy	97 (49%)	8 (4%)	83 (63%)	4 (3%)	14 (22%)	4 (6%)
Year of pregnancy	2004 (18)	0	2009 (10)	0	1989 (10)	0
1979-1989	37 (19%)					
1990-1999	44 (22%)					
2000-2009	54 (27%)					
2010-2017	62 (32%)					
Pre-pregnancy BMI	25 (±4)	70 (36%)	25(±4)	33 (25%)	23 (±2)	37 (57%)
Primipara at first pregnancy after KT	154 (78%)	5 (3%)	100 (76%)	2 (2%)	54 (83%)	3 (5%)
Preterm < 37 weeks	102 (52%)	13 (7%)	77 (58%)	4 (3%)	25 (39%)	9 (14%)
Preterm < 34 weeks	50 (25%)					

Appendix 2B: Characteristics of all 1st pregnancies (n=197) before and after 1990 *Continued*

	Total group N = 197		Transplanted ≥ 1990 = 132		Transplanted < 1990 N = 65	
	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*	N (%)*/ Mean ±SD	Missing N (%)*
Birthweight (gram)	2281 (±853)	13 (7%)	2174 (±928)	5 (4%)	2520 (±597)	8 (12%)
Low birthweight (<2500 gram)	103 (52%)		76 (58%)		27 (42%)	
Very low birthweight (<1500 gram)	30 (15%)		27 (21%)		3 (5%)	
Gestational hypertension	90 (46%)	37 (19%)	69 (52%)	15 (11%)	21 (32%)	22 (34%)
Severe hypertension	30 (15%)	56 (28%)	22 (17%)	29 (22%)	8 (12%)	28 (43%)
Preeclampsia	60 (31%)	32 (16%)	49 (37%)	12 (9%)	11 (17%)	20 (31%)
% Scr decrease during pregnancy	17 (±10)	45 (23%)	17 (±10)	22 (17%)	15 (±11)	25 (38%)
> 15% Scr decrease during pregnancy	90 (46%)		67 (51%)		21 (32%)	

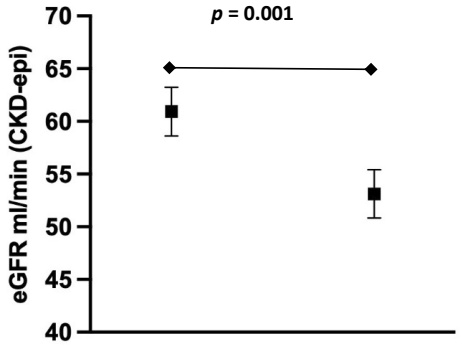
KT: kidney transplantation (last KT before pregnancy), eGFR: estimated Glomerular Filtration Rate, ESRD: end stage renal disease, MAP: mean arterial pressure, CNI: calcineurine inhibitors, BMI: body mass index, SCr: serum creatinine, SD: standard deviation * Due to rounding it can be possible that percentages not reach 100%, **Median (IQR)

Appendix 3: Declaration of missing subjects per pregnancy interval

Missing	**Pregnancy interval 0**			**Pregnancy interval 1**		
Reasons for missing pregnancy interval 0				**Reasons for missing pregnancy interval 1**		
1	R-27 unknown/check-ups non-academic hospital	E-22 Conception within 6months after KT	L-4 unknown/check-ups non-academic hospital	E-7 Short time period between 1st and 2nd preg after KT	A-2 Graft loss during pregnancy	L-23 Short time period between 1st and 2nd preg after KT
2	R-14 Conception within 6 months after. KT	L-22 unknown/check-ups non-academic hospital	L-24 unknown/check-ups non-academic hospital	E-17 Short time period between 1st and 2nd preg after KT	A-18 Lost to follow-up after pregnancy	
3	L-5 unknown/check-ups non-academic hospital	R-9 Conception within 6months after KT	R-24 unknown/check-ups non-academic hospital	E-29 Short time period between 1st and 2nd preg after KT	E-8 DCGL before annual eGFR measurement	
4				L-13 Short time period between 1st and 2nd preg after KT	L-33 Death before annual eGFR measurement	
5				L-23 Short time period between 1st and 2nd preg after KT	R-6 recent pregnancy no follow up yet	
7				M-5 Short time period between 1st and 2nd preg after KT	R-8 recent pregnancy nn follow up yet	

Appendix 3: Declaration of missing subjects per pregnancy interval *Continued*

Missing	**Pregnancy interval 0**			**Pregnancy interval 1**		
Reasons for missing pregnancy interval 0				**Reasons for missing pregnancy interval 1**		
8				R-1 Short time period between 1st and 2nd preg after KT	R-35 unknown/check-ups non-academic hospital	
9				G-41 Short time period between 1st and 2nd preg after KT		
10				G-44 Short time period between 1st and 2nd preg after KT		
Included	**Pregnancy interval 1& 2**	**Pregnancy interval 1**	**Pregnancy interval 2**	**Pregnancy interval 0 & 2**	**Pregnancy interval 0**	**Pregnancy interval. 0, 2 & 3**
Total number of included eGFR measurements	**18**	**53**	**31**	**132**	**36**	**11**



Characteristics per pregnancy interval	Before 1st pregnancy (0)	After 1st pregnancy (1)
Women included	105	100
Total nr. of eGFR	681	796
Median nr. of eGFR per woman (IQR)	6 (4)	5 (9)
Median yrs between first and last eGFR (IQR)	2.09 (4.22)	6.14 (10.20)
Mean eGFR slope (compared to interval 0)	Reference	-7.81 ml/min/1.73m^2 (p=0.001)

Appendix 4: Adjusted mean eGFR before and after pregnancy after kidney transplantation (GEE)

Only women with one pregnancy after kidney transplantation (n=109)
GEE: generalized estimated equations; a multilevel method. KT: kidney transplantation (last KT before pregnancy);
eGFR: estimated Glomerular Filtration Rate. *median (IQR). Subject level: subject ID, Within-subject level: days after KT. In the model, years after KT was used as a continuous covariate and pregnancy interval as a categorical factor. Error bars illustrate standard deviation (SD)**.** eGFR during pregnancy was excluded.

Appendix 5: Multivariate analysis with adverse pregnancy outcomes.

	B coëfficiënt	Standard error of the mean (SEM)	p-value
After first pregnancy	-0.73	3.41	0.83
Year of KT ≥ 1990	2.83	2.44	0.25
Transplant vintage (years)	**-1.00**	**0.24**	**<0.01**
Age at KT	0.03	0.22	0.90
Primipara	0.62	2.81	0.83
Rejection before 1st pregnancy	**-2.90**	**1.65**	**0.08**
KT to 1st conception interval (years)	**1.20**	**0.27**	**<0.01**
Pre-pregnancy eGFR (1st pregnancy)	**0.82**	**0.06**	**<0.01**
Pre-pregnancy hypertension (1st pregnancy)	-1.31	2.35	0.58
CNI before 1st pregnancy	0.62	1.59	0.70
Gestational hypertension	-0.09	3.40	0.98
Low birthweight <2500 gram	-0.82	3.13	0.80
> 15% SCr decrease during pregnancy	-0.30	3.22	0.93

For this analysis a dichotomous variable 'After first pregnancy' was created (before or after pregnancy). After pregnancy means all eGFR measurements after 1st pregnancy (pregnancy interval 1), after 2nd pregnancy (pregnancy interval 2) and after 3rd pregnancy (pregnancy interval 3). eGFRs during pregnancy and within 6 months after delivery were excluded.
eGFR: estimated Glomerular Filtration Rate, CNI: calcineurin inhibitor, GEE: generalized estimated equations, KT: kidney transplantation

Chapter 4

A nationwide Dutch cohort study shows relatively good pregnancy outcomes after kidney transplantation and finds risk factors for adverse outcomes

Margriet E. Gosselink, Marleen C. van Buren, Judith Kooiman, Henk Groen, Wessel Ganzevoort, Henk W. van Hamersvelt, Olivier W.H. van der Heijden, Jacqueline van de Wetering, A. Titia Lely

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Nationwide Pregnancy Outcomes After Kidney Transplantation And Prediction Of Adverse Pregnancy Outcomes: a Dutch Cohort Study

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

STUDY DESIGN & METHODS

Netherlands 1971-2017

Retrospective cohort KT:
- Pregnancy > 20 weeks
- Analyses per prepregnancy eGFR-CKD-category

Combined adverse pregnancy outcome (cAPO):
- Birthweight <2500 gram
- Preterm birth <37 weeks
- Severe hypertension
- >15% graft deterioration during pregnancy

Results (1)

Cohort: 288 pregnancies

- Live birth rate 93%
- Mean gestational age 35.6 weeks
- Mean birthweight 2383 gram

Results (2)

Independent risk factors cAPO:
1. Prepregnancy eGFR *(OR 0.98 (95% CI 0.96–0.99)*
2. Midterm percentage SCr dip *(OR 0.95, 0.91-0.98)*
3. Midterm MAP dip *(OR 0.94, 0.90-0.98)*

- cAPO risk indicator for graft loss *(HR 2.55, 1.09-5.96)*
- No significant risk factor if corrected for prepregnancy eGFR *(HR 2.18, 0.92-5.13)*.

Gosselink, 2022

CONCLUSION

- Novel analysis per eGFR-CKD-category, including advanced CKD-stages
- Prepregnancy graft function and hemodynamic adaptation to pregnancy most important risk factors for adverse outcomes

ABSTRACT

Although numbers of pregnancy after kidney transplantation (KT) are rising, high risks of adverse pregnancy outcomes (APO) remain. Though important for pre-conception counseling and pregnancy monitoring, analyses of pregnancy outcomes after KT per pre-pregnancy estimated glomerular filtration rate-chronic kidney disease (eGFR-CKD)-categories have not been performed on a large scale before. To do this, we conducted a Dutch nationwide cohort study after consecutive singleton pregnancies over 20 weeks of gestation after KT. Outcomes were analyzed per pre-pregnancy eGFR-CKD-category and a composite APO (cAPO) was established including birthweight under 2500 gram, preterm birth under 37 weeks, third trimester severe hypertension (systolic blood pressure over 160 and/or diastolic blood pressure over 110 mmHg) and/or over 15% increase in serum creatinine during pregnancy. Risk factors for cAPO were analyzed in a multilevel model after multiple imputation of missing predictor values. In total, 288 pregnancies in 192 women were included. Total live birth was 93%, mean gestational age 35.6 weeks and mean birthweight 2383 gram. Independent risk factors for cAPO were pre-pregnancy eGFR, midterm percentage serum creatinine dip and midterm mean arterial pressure dip; odds ratio 0.98 (95% confidence interval 0.96–0.99), 0.95 (0.93-0.98) and 0.94 (0.90-0.98), respectively. The cAPO was a risk indicator for graft loss (hazard ratio 2.55, 1.09-5.96) but no significant risk factor on its own when considering pre-pregnancy eGFR (2.18, 0.92-5.13). This was the largest and most comprehensive study of pregnancy outcomes after KT, including pregnancies in women with poor kidney function, to facilitate individualized pre-pregnancy counseling based on pre-pregnancy graft function. Overall obstetric outcomes are good. The risk of adverse outcomes is mainly dependent on pre-pregnancy graft function and hemodynamic adaptation to pregnancy.

INTRODUCTION

The first successful pregnancy after KT was reported in 1958.[1] Today, about 6/100 000 births in the US result from pregnancies in women with a KT, corresponding to 227 births annually.[2,3] Although the annual numbers of pregnancy after kidney transplantation (KT) are rising, challenges remain prominent. High incidences of adverse pregnancy outcomes such as preeclampsia, hypertensive disorders of pregnancy, fetal growth restriction and preterm birth have been reported.[4-6] Although previous studies on pregnancy outcomes in women with CKD and after KT have been conducted[7-10], data on pregnancy outcomes after KT analysed per consecutive prepregnancy eGFR-CKD-category (including advanced stages)[11] on a large scale is still missing. This is essential information for prepregnancy counseling. Furthermore, previous studies investigating risk factors for adverse pregnancy outcomes are limited to voluntary registries, a selected group of patients or missing data.[10,12] Therefore, this study aims to analyse risks of adverse pregnancy outcomes after KT -depending on prepregnancy eGFR-CKD-category- and to identify risk factors for adverse outcomes in a large nationwide cohort.

METHODS

Study design & participants

We performed a retrospective cohort study using patient data originating from the PARTOUT-network (Pregnancy After Renal Transplantation OUTcomes-network). The PARTOUT-network was established in 2017 by a collaboration between obstetricians and transplant nephrologists in all eight kidney transplant centres in the Netherlands. Consecutive pregnant kidney transplant recipients (KT-recipients) transplanted between 1971 and 2017 were identified via a systematic search in the National Organ Transplant Registry (NOTR). In this registry, all transplanted patients in the Netherlands are registered. With lacking information on pregnancy after KT, the NOTR was only used for patient identification and not for data collection. The patient search was completed with questioning transplant nephrologists and gynaecologists in participating centres. Of note, KT and care for pregnancies after KT is centred in university medical centres in the Netherlands. Therefore, the PARTOUT-network aimed for nationwide consecutive inclusion.

Patients were eligible for inclusion in case of an ongoing singleton pregnancy of >20 weeks of gestation in adult KT-recipients. Twin pregnancies were excluded because of a higher incidence of maternal and neonatal complications.[13,14] Data was collected until December 31st, 2017.

This study was approved by the Medical Ethics Committee of all Dutch transplant centers (MEC-2016-634, 16-021/C, G16.014,2015-2262).

Data collection and definitions

A dedicated medical research team anonymized and retrospectively collected data by scrutinizing medical charts. The data was registered using standardized case record forms (Open Clinica open source software, version 3.1).[15] Baseline characteristics including information on underlying kidney disease, KT, obstetric history, transplant-conception interval (TCI) and use of medication were collected. Prepregnancy eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[16] Furthermore, obstetric and neonatal outcomes were collected. Conception date was calculated as 280 days before the estimated date of delivery by ultrasound or estimated last menstrual period. Small for gestational age (SGA) was defined as birthweight below the 5th or 10th percentile on the national birth weight charts.[17] Perinatal mortality was defined as stillbirth from 28 weeks of pregnancy or neonatal death < 7 days after birth.[18] This study excluded spontaneous pregnancy loss <20 weeks due to the possibility of recording bias. Therefore, live birth rates concern pregnancies >20 weeks of gestation.

SCr values were documented both prepregnancy, by selecting the closest outpatient clinic value prior to conception, and during each trimester of pregnancy. When multiple values in one trimester were measured, the mean was calculated and considered for analysis. Also, the lowest SCr value between 8 and 20 weeks was collected. In a comparable manner blood pressure values were collected. Regarding severe hypertension, highest measured levels were selected. All values were checked by transplant nephrologists and/or gynaecologists to ensure representivity.

Data on antihypertensive and immune suppressive medication was collected. No further analyses on antihypertensive treatment were performed because of missing data and the known poor validity of registered medication, with discrepancies between prescription, dispense and therapy adherence.[19-21] Rejection was defined as having a biopsy proven rejection or treatment for rejection by clinical diagnosis.

Chronic hypertension was defined according to the National Institute for Health and Care Excellence (NICE) guideline as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication at conception. Gestational hypertension (novel or superimposed) was defined similar to chronic hypertension, only occurring at >20 weeks of gestation.[22] With a lacking proper definition for preeclampsia in women with CKD, (superimposed) preeclampsia in obstetric history or during pregnancy was defined by the attending physician at time of pregnancy, by the presence of hypertension >20 weeks of gestation and

proteinuria.[23] This could not be uniformly defined retrospectively because of missing proteinuria values. Furthermore, obstetric and nephrological care during pregnancy was at the discretion of the treating physicians, guided by institutional policy and practice. Mean arterial pressure (MAP) was calculated from mean SBP and DBP-values. Midterm blood pressure drop was defined as the absolute difference between MAP during second trimester of pregnancy and prepregnancy MAP.[24-27] Midterm renal hyperfiltration was assessed by studying the absolute (in µmol/L) and percentage (%)-dip in SCr between 8 and 20 weeks of gestation compared to prepregnancy SCr.[28,29]

Study Endpoints

The primary outcomes of our study were pregnancy outcomes after KT sorted by prepregnancy eGFR-CKD-category. Due to low event rates in maternal outcomes, a composite adverse pregnancy outcome (cAPO) was established incorporating severe hypertension in third trimester (i.e. >160 mmHg systolic BP and/or >110 mmHg diastolic BP), increase of >15% of SCr in the third trimester as compared with prepregnancy values, birthweight <2500 gram or preterm birth (gestational age < 37 weeks).[22,30,31]

Patients were lost to follow-up on the composite endpoint when 1) data was missing on all four components or 2) ≥1 of the individual components were missing and other components of the composite endpoint were scored negative. These pregnancies could not be analysed in prediction analysis.

Patients were included over a long time in which policy changes occurred, such as the wide introduction of calcineurin inhibitors (CNI) in the 1990s, prescription of acetylsalicylic acid for preeclampsia risk reduction,[22,32] different blood pressure targets[22,33] and the more liberal policy of 'allowing' pregnancy after KT in less ideal situations.[34-36] Therefore, baseline characteristics and pregnancy outcomes were stratified per decennium and per prescription of CNI (cyclosporine (CyA) and tacrolimus). Furthermore, transplant-era ('before introduction of CyA' (<1990) and 'after introduction of CyA and tacrolimus' (>1990)) and decennium were assessed in prediction analysis.

The PARTOUT-network investigated pregnancy outcomes stratified per use of CNI earlier.[37] Therefore, we only provide an overview of baseline characteristics and outcomes of CNI use and a compact prediction analysis. Likewise, the influence of pregnancy on graft loss was earlier investigated and therefore only concisely investigated in this study.[34]

Statistical analysis

Since women were allowed to contribute with ≥1 pregnancy to the cohort, the experimental unit for all analyses was on a pregnancy level. Continuous variables were reported as means (SD) in case of a normal distribution. Variables with skewed distribution were reported as median with interquartile range (IQR). Study endpoints were reported as incidence proportions (95% CI). To allow for the non-independence of multiple pregnancies in one woman, the data had a multilevel structure and was analysed using generalized estimating equation (GEE). This is an established method for multilevel analysis.

Pregnancy outcomes per prepregnancy eGFR-CKD-category were analysed for the total cohort. Variables associated with the composite adverse pregnancy outcome were initially identified by univariable GEE-analysis, followed by multilevel GEE to assess independency of the associations. Of note, the association between possible predictors and the composite adverse pregnancy outcome were analysed without building a prediction model. Odds ratios (ORs) with corresponding 95% confidence intervals (CI) were calculated. Univariable GEE analyses were performed using an unstructured correlation matrix structure. For multivariable analyses, an exchangeable correlation matrix structure was used. Prior to prediction analyses, missing predictor values were imputed to avoid only including the complete cases for analysis.[38]

Multiple imputation was performed with 20 imputations rounds. Distribution of predictors prior to and following imputation were compared to check for imbalances. Candidate predictors for the adverse pregnancy outcome were selected based on previous literature and included maternal age, body mass index (BMI), transplantation conception interval, decennium, transplant-era, prepregnancy eGFR, obstetric history (i.e. preterm birth, preeclampsia), prepregnancy hypertension, midterm MAP drop and midterm SCr drop.[28,29,39-41] Also, the pattern of change in blood pressure and SCr-values during pregnancy were assessed, comparing complicated pregnancies to not-complicated pregnancies.

Lastly, the risk of graft loss after pregnancies with the composite adverse pregnancy outcome was investigated with Kaplan-Meier and multivariable Cox Regression survival analyses. Death censored graft loss was calculated from the transplantation date to the date of irreversible graft failure or the last follow-up date with functioning graft until 31st December 2017. When death occurred with a functioning graft, the period of follow-up was censored at the date of death. The risk of graft loss after pregnancies with the composite adverse pregnancy outcome was corrected for the influence of known risk factors for graft loss such as prepregnancy eGFR, hypertension before pregnancy, acute rejection before first pregnancy, retransplantation before pregnancy, dialysis before KT and type of KT.[42-47] P-values below 0.05

were regarded as statistically significant for all analyses. Analyses were performed using IBM SPSS Statistics version 25.0.0 (SPSS Inc) and Graph Pad Prism version 8.4.1 (Graph Pad Software Inc).

RESULTS

Between 1971 and 2017, 301 pregnancies after KT were registered in 202 women. After exclusion of 13 twin pregnancies, 288 singleton pregnancies were included for analysis. Baseline characteristics and pregnancy outcomes of twin pregnancies are shown in the supplementary file (Table S1 and S2). Prediction analysis for adverse pregnancy outcomes was carried out in 237 patients.(**Figure 1**) Baseline characteristics of our study population are reported in **Table 1**, structured per prepregnancy eGFR-CKD-category. Overall, the occurrence of pregnancy after KT in the Netherlands increased during our study period per decennium from 16.81 per 100 000 singleton live births in the eighties to 47.53 in the last decennium.

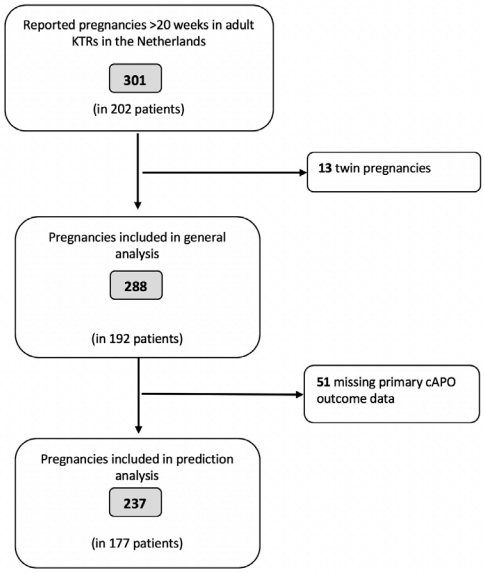


Figure 1: Flowchart of this study

Consecutive pregnancies in KT-recipients between 1971 and 2017 were identified via the National Organ Transplant Registry (NOTR) and via transplant nephrologists in all university medical centres in the Netherlands, ensuring nationwide consecutive inclusion. Patients were eligible for inclusion in case of an age above 18 years and an ongoing singleton pregnancy of at least 20 weeks of gestation after KT. After first inclusion, twin pregnancies were excluded. For prediction analysis pregnancies with missing outcome cAPO data were excluded.

Table 1. Baseline characteristics, total and divided per prepregnancy eGFR-CKD-category

Variable	All pregnancies *N= 288*	eGFR ≥ 90 ml/min/1.73m² *N = 23*	eGFR 90 – 60 ml/min/1.73m² *N = 104*	eGFR 59 – 45 ml/min/1.73m² *N = 72*	eGFR 44 – 30 ml/min/1.73m² *N = 44*	eGFR <30 ml/min/1.73m² *N = 10*
Cause of kidney failure						
Glomerulonephritis	97/258 (38%)	9/23 (39)	35/92 (38)	22/62 (35)	15/40 (38)	5/9 (56)
Interstitial	44/258 (17%)	5/23 (22)	15/92 (16)	10/62 (16)	5/40 (13)	0
Diabetes	6/258 (2%)	3/23 (13)	2/92 (22)	1/62 (2)	0	0
Auto-immune	11/258 (4%)	0	2/92 (22)	3/62 (5)	3/40 (8)	0
Other	100/258 (39%)	6/23 (26)	38/92 (41)	26/62 (42)	17/40 (43)	4/9 (44)
History of multiple transplantations	61/288 (21%)	4/23 (17%)	28/104 (27%)	13/72 (18%)	4/44 (9%)	5/10 (50%)
2	53/288 (18%)	3/23 (13%)	22/104 (21%)	13/72 (18%)	3/44 (7%)	5/10 (50%)
3	8/288 (3%)	1/23 (4%)	6/104 (6%)	0	1/44 (2%)	0
Type of transplant, Living donor	111/271 (41%)	5 (22%)	43 (42%)	35 (51%)	21 (48%)	2 (20%)
Pregnancy before KT	49/280 (18%)	3/23 (13%)	15/100 (15%)	14/69 (20%)	7/44 (16%)	4/9 (44%)
History of preterm birth before KT	18/49 (37%)	1/3 (33%)	5/15 (33%)	5/14 (36%)	3/7 (43%)	3/4 (75%)
History of (superimposed) preeclampsia before KT	10/49 (20%)	1/3 (33%)	4/15 (27%)	3/14 (21%)	0 (0%)	1/4 (25%)
Multiple pregnancies after KT	96/288 (33%)	9/23 (39%)	33/104 (32%)	24/72 (33%)	13/44 (30%)	3/10 (30%)
2	89/288 (31%)	8/23 (35%)	32/104 (31%)	22/72 (31%)	12/44 (27%)	2/10 (20%)
3	7/288 (2%)	1/23 (4%)	1/104 (1%)	2/72 (3%)	1/44 (2%)	1/10 (10%)
Median transplant conception interval, years (IQR)	5 (7)	5 (9)	6 (7)	4 (5)	6 (6)	5 (4)
Caucasian race	174/207 (84%)	11/15 (73%)	66/78 (85%)	40/48 (83%)	37/40 (93%)	6/8 (75%)

Table 1. Baseline characteristics, total and divided per prepregnancy eGFR-CKD-category *Continued*

Variable	All pregnancies *N= 288*	eGFR ≥ 90 ml/min/1.73m² *N = 23*	eGFR 90 – 60 ml/min/1.73m² *N = 104*	eGFR 59 – 45 ml/min/1.73m² *N = 72*	eGFR 44 – 30 ml/min/1.73m² *N = 44*	eGFR <30 ml/min/1.73m² *N = 10*
Age at pregnancy (IQR)	31 (5)	32 (6)	31 (5)	31 (7)	32 (5)	33 (5)
Median BMI at pregnancy (IQR)	24 (5)	22,6 (4)	24,4 (5)	24,4 (6)	23,1 (4)	23,6 (1)
Chronic hypertension	147/251 (59%)	6/21 (29%)	46/89 (52%)	40/67 (60%)	33/40 (83%)	8/10 (80%)
Prepregnancy serum creatinine, µmol/L	117 (57)	68 (8)	91 (9)	120 (9)	156 (18)	310 (160)

Data are presented as mean (SD) and n (%) unless stated otherwise. Not all baseline characteristics were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases are described here: *Age at pregnancy: n = 275. TCI: n = 269; prepregnancy serum creatinine: n = 257; BMI at pregnancy: n = 180. Gestational age: n = 265; Birthweight: n = 261.* SBP = systolic blood pressure, DBP= diastolic blood pressure, BMI = body mass index. eGFR calculated with the CKD-EPI method, categories corresponding to Chronic Kidney Disease stages.

Table 2. Study outcomes, total and divided per prepregnancy eGFR-CKD-category

Variable	All pregnancies *N= 288*	eGFR ≥ 90 ml/min/1.73m² *N = 23*	eGFR 89 – 60 ml/min/1.73m² *N = 104*	eGFR 59 – 45 ml/min/1.73m² *N = 72*	eGFR 44 – 30 ml/min/1.73m² *N = 44*	eGFR <30 ml/min/1.73m² *N = 10*
Neonatal outcomes						
Gestational age, days (SD)	249 (30)	264 (18)	253 (27)	244 (32)	241 (33)	221 (32)
Gestational age, weeks	35.6	37.7	36.1	34.9	34.4	31.6
Preterm birth*	132/265 (50%, 42 to 59%)	7/22 (32%)	41/99 (41%)	42/71 (59%)	25/42 (60%)	9/10 (90%)
<34 weeks	64/265 (24%, 19 to 31%)	2/22 (9%)	14/99 (14%)	23/71 (32%)	16/42 (38%)	6/10 (60%)
<28 weeks	18/265 (7%, 4 to 11%)	0	5/99 (5%)	4/71 (6%)	6/42 (14%)	2/10 (20%)
Birth weight, gram (SD)	2383 (885)	2846 (753)	2512 (724)	2388 (940)	2087 (937)	1335 (725)
<2500 gram	129/261 (49%, 43 to 55%)	6/21 (29%)	42/96 (44%)	32/69 (46%)	28/41 (68%)	10/10 (100%)
<1500 gram	41/261 (16%, 11 to 21%)	1/21 (5%)	7/96 (7%)	13/69 (19%)	11/41 (27%)	6/10 (60%)
Percentile corrected for gestational age (IQR)	13 (46)	27 (41)	21 (45)	18 (63)	8,5 (33)	4,5 (12)
Small for gestational age						
< p10	102/243 (42%, 34 to 51%)	8/21 (38%)	33/90 (36%)	25/65 (39%)	21/40 (53%)	7/10 (70%)
< p5	64/243 (26%, 20 to 34%)	4/21 (19%)	22/90 (40%)	18/65 (28%)	10/40 (25%)	5/10 (50%)
Apgar <=5, 5 minutes after birth	15/180 (8%)	2/14 (14%)	3/65 (5%)	2/50 (4%)	4/31 (13%)	1/9 (11%)
NICU admission	28/202 (14%)	2/23 (9%)	8/104 (8%)	9/72 (13%)	5/44 (11%)	4/9 (44%)

Table 2. Study outcomes, total and divided per prepregnancy eGFR-CKD-category *Continued*

Variable	All pregnancies *N= 288*	eGFR ≥ 90 ml/min/1.73m² *N = 23*	eGFR 89 – 60 ml/min/1.73m² *N = 104*	eGFR 59 – 45 ml/min/1.73m² *N = 72*	eGFR 44 – 30 ml/min/1.73m² *N = 44*	eGFR <30 ml/min/1.73m² *N = 10*
Stillbirth	19/282 (7%, 4 to 10%)	0	4/103 (4%)	6/71 (8%)	4/44 (9%)	0
Neonatal mortality (in first 7 days of life)	8/255 (3%, 2 to 6%)	1/23 (4%)	1/97 (1%)	2/64 (2%)	1/38 (3%)	2/9 (22%)
Maternal outcomes						
Gestational hypertension	61/233 (26%, 21 to 32%)	6/17 (35%)	42/86 (49%)	39/63 (62%)	23/39 (59%)	4/6 (67%)
(Superimposed) preeclampsia	81/235 (34%, 29 to 41%)	7/18 (39%)	33/85 (39%)	21/67 (31%)	13/40 (33%)	8/8 (100%)
Rejection therapy during pregnancy	3/227 (1%, 0.3 to 3.9%)	0	2/83 (2%)	0	1/38 (3%)	0
Use of calcineurine inhibitor during pregnancy	143/275 (50%)	6/21 (29%)	43/100 (43%)	40/71 (56%)	32/44 (73%)	6/10 (60%)
Cyclosporin	79/275 (29%)	3/21 (14%)	25/100 (25%)	25/70 (36%)	19/44 (43%)	2/10 (20%)
Tacrolimus	62/275 (23%)	3/21 (14%)	17/100 (17%)	14/70 (20%)	13/44 (30%)	4/10 (40%)
Composite Adverse Pregnancy Outcome	186/237 (78%, 68 to 91%)	13/21 (62%)	60/83 (72%)	50/64 (78%)	37/43 (86%)	10/10 (100%)

Incidences are shown as numerator/denominator(frequency, 95% CI) of pregnancies with available composite outcome data. Not all pregnancy outcomes were available for every patient. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases are described here: *gestational age, n = 265. Percentile corrected for gestational age, n = 243*

Variables that are part of the composite outcome are marked with an asterisk. eGFR calculated with the CKD-EPI method, categories corresponding to Chronic Kidney Disease stages

Neonatal outcomes

In **Table 2** the study outcomes for the total cohort are shown. The total live birth rate ≥20 weeks of gestation was 93%. Neonatal death occurred in 8/255 (3%) of pregnancies, of which 5/8 (63%) occurred before the year 2000 and 3/8 (38%) in the period after 2000. Preterm birth occurred in 50% of pregnancies. Mean gestational age was 249 days (SD 30, 35.6 weeks). For preterm births, mean duration of pregnancy was 230 days (SD 29), 32.9 weeks. Mean birthweight was 2383 (SD 885) gram, corresponding to a median percentile corrected for gestational age of 13 (IQR 46). Birthweight <2500 gram was seen in 49% of pregnancies. 15/180 (8%) of babies had Apgar-scores ≤5 5 minutes after delivery and 28/202 (14%) were admitted to a Neonatal Intensive Care Unit (NICU). For these parameters a large amount of missing values existed (35% for Apgar-scores and 30% for NICU admission). Lower prepregnancy eGFR-categories showed a shorter duration of pregnancy and a lower birth weight.

Maternal outcomes

Hypertensive disorders of pregnancy were common, with 26% of pregnancies complicated by gestational hypertension and 34% by (superimposed) preeclampsia. Overall, mean SBP increased over time from 122 mmHg (SD 10.5) in the first trimester to 123 mmHg (SD 11.6) in the second and 129 mmHg (SD 12.9) in the third trimester. In 163/231 (71%) (missing data 20%) of pregnancies antihypertensive medication was used. In Table S3 and S4 a summary of antihypertensive and immune suppressive medication during pregnancy is shown. During pregnancy, use of antihypertensive medication increased. Of all pregnancies with antihypertensive medication use, 132/163 (59%) used medication during the first trimester, 138/163 (85%) during the second and 151/153 (99%) during the third. The use of triple medication increased from 3% during 1st trimester, to 6% during second and 13% during third. Almost all pregnancies with triple medication in the third trimester scored positive on our combined adverse pregnancy outcome (19/20). Mean prepregnancy eGFR was 61 ml/min/1.73m^2 (SD 21). Median time between prepregnancy SCr measurement and conception was 37 days (IQR 56). Mean SCr was 108 µmol/l (SD 51.4) during the first trimester, 108 µmol/l (SD 58.1) during the second and 120 µmol/l (SD 53.7) during the third trimester.

Caesarean section occurred in 48% of pregnancies. Of preterm births, 41% were vaginal deliveries, of which 58% were induced, as well as 10% of caesarean sections. Iatrogenic preterm birth increased over time (Table S5,6) and occurred in 79% of preterm pregnancies.

Transplant-eras and decades

Baseline characteristics and pregnancy outcomes stratified per decennium and per use of CNI are shown in Table S5, S6, S7 and S8. Per decade of pregnancy, the incidence of living donor transplants was higher, prepregnancy eGFR was lower and the use of CNI increased. In pregnancies within the transplant-era 'after CyA and tacrolimus' and with use of CNI, more gestational hypertension occurred (61% versus 45%) but this was no longer significant when corrected for prepregnancy eGFR (p = 0.08). The incidences of low birth weight and preterm birth did not differ significantly.

Predictors of the combined adverse pregnancy outcome (cAPO)

Results of the univariable and multivariable multilevel analyses are presented in **Table 3**.

In pregnancies with complete follow-up, the composite adverse pregnancy outcome was observed in 186/237 (78%) pregnancies (Table S9). Baseline characteristics of pregnancies included in prediction analysis are shown in Table S10. Pregnancies with missing data on the composite endpoint are reported in Table S11. As shown in Table S10, pregnancies with the composite adverse pregnancy outcome had a lower prepregnancy eGFR. As shown in Table S11, pregnancies with missing data on the composite endpoint had a generally lower baseline risk of adverse pregnancy outcomes, with lower incidences of PE and preterm birth in obstetric history, higher prepregnancy eGFR levels and a lower incidence of chronic hypertension. After multiple imputation for missing predictor values, data of imputed variables showed a similar overall distribution compared with the observed data.(Table S12, Figure S1)

Table 3. Uni- and multivariable analysis of predictors of the composite adverse pregnancy outcome

Predictor	Odds Ratio	95% CI
Univariable analysis		
Age at pregnancy, years	1,020	0,961 to 1,083
BMI at pregnancy, kg/m^2	1,013	0,929 to 1,105
Transplant – conception interval, years	1,020	0,950 to 1,096
Hypertension before pregnancy	1,100	0,547 to 2,212
eGFR prepregnancy*, ml/min/1.73 ^{m2}	0,980	0,966 to 0,994
Percentage SCr drop*, %	0,963	0,935 to 0,991
MAP prior to pregnancy, mmHg	0,993	0,957 to 1,029
MAP drop 2nd trimester*, mmHg	0,942	0,908 to 0,977

Table 3. Uni- and multivariable analysis of predictors of the composite adverse pregnancy outcome *Continued*

Predictor	Odds Ratio	95% CI
Cadaver kidney transplant	0,965	0,500 to 1,860
Diagnosis kidney disease before KT		
Glomerulonephritis	1,255	0,499 to 3,158
Other	0,984	0,404 to 2,396
History of preterm birth	1,452	0,427 to 4,938
History of preeclampsia	1,134	0,248 to 5,186
Multipara	0,133	0,461 to 1,448
Decade of delivery		
1980 – 1990	2,522	0,674 to 9,431
1990 – 2000	1,192	0,494 to 2,881
2000 – 2010	0,670	0,324 to 1,386
2010 – 2017	Reference	Reference
Transplant era		
Before CyA (<1990)	2,484	0,736 to 8,373
After CyA and tacrolimus (>1990)	Reference	Reference
Multivariable analysis		
eGFR prepregnancy, ml/min/1.73 m^2*	0,977	0,961 to 0,993
Percentage SCr drop, %*	0,953	0,925 to 0,981
MAP drop 2nd trimester, mmHg*	0,938	0,901 to 0,976

Percentage SCr drop = percentual drop between the lowest SCr 8-20 weeks and prepregnancy SCr. *= statistically significant, p-value <0.05

When comparing cAPO to no-cAPO-pregnancies, mean mid-term MAP drop was significantly smaller in pregnancies with the composite adverse pregnancy outcome, mean difference -6,1 (SD 24.6), p-value 0.001.(**Figure 2**) Also, mid-term percentage SCr dip was significantly smaller in pregnancies with the composite adverse pregnancy outcome, mean difference -4,5%, p-value 0.003.(**Figure 2**). As shown in **Table 3**, from the candidate predictors available at preconception counseling, only prepregnancy eGFR was identified as an independent predictor for the composite adverse pregnancy outcome with OR 0.98 (95% CI 0.96 to 9.99). During pregnancy, midterm MAP dip and midterm percentage SCr dip were independent predictors for the composite adverse pregnancy outcome with corresponding ORs of 0.95 (95% CI 0.93 to 0.98) and 0.94 (95% CI 0.90 to 0.98). Decade of pregnancy and 'transplant-era' had no significant association with the composite adverse pregnancy outcome.

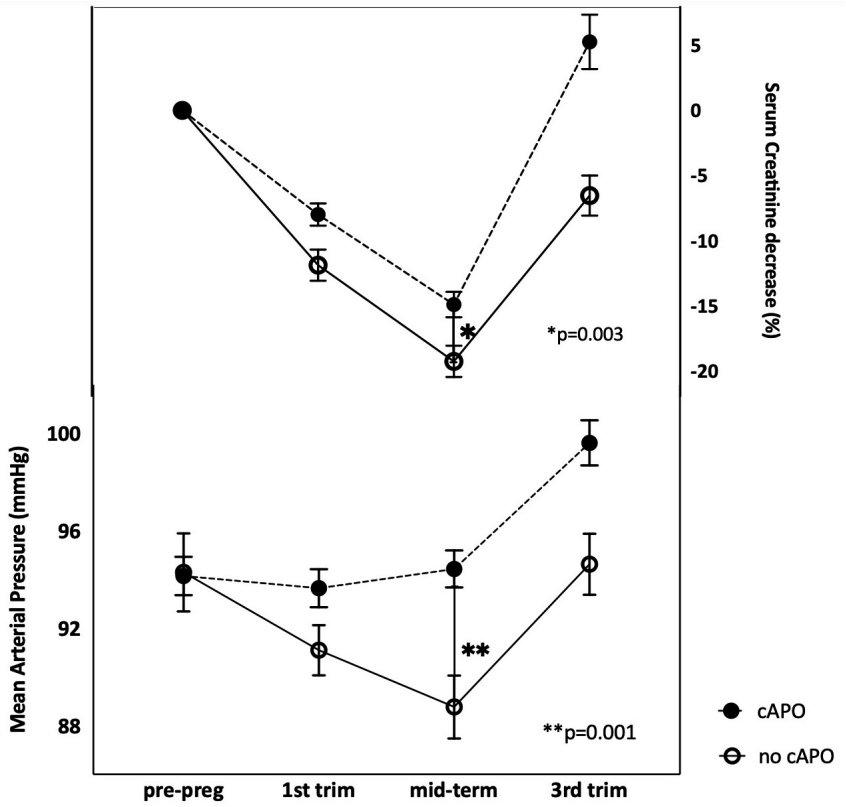
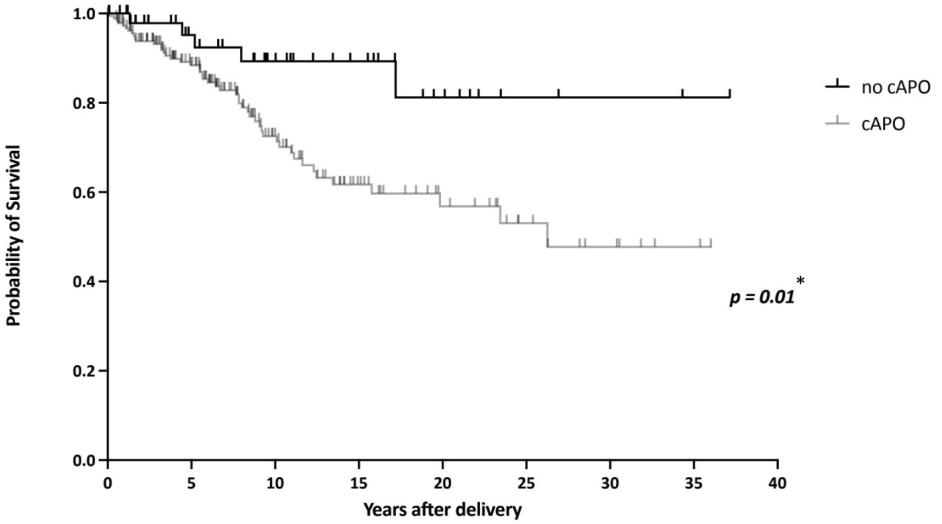


Figure 2: Serum Creatinine and Mean Arterial Pressure (MAP) during pregnancy after KT

cAPO pregnancies compared to no cAPO. Data are presented as mean (SEM). P-values are shown for the midterm delta MAP (absolute) and SCr decrease (%)

Risk of graft loss after pregnancy

Median follow-up time after pregnancy for the outcome of graft loss was 7.9 years (IQR 12.2). Graft loss occurred in 23% (95% CI 19 to 28%) of pregnancies with a median time after delivery of 6.44 years (IQR 8.43). In univariate analysis, the composite adverse pregnancy outcome showed to be a significant risk indicator for graft loss (HR 2.55, 95% CI 1.09 to 5.96). (**Figure 3**). After correction for prepregnancy eGFR the overall effect was similar, but no longer significant (HR 2.18 (95% CI 0.92 to 5.13).



Nrs. at risk									
cAPO no	51	35	23	16	9	4	3	2	0
cAPO yes	186	121	61	34	21	12	7	3	0

*Log rank (Mantel-Cox) test

Figure 3: Death Censored Graft Loss in years after delivery in Kidney Transplant Recipients combined Adverse Pregnancy Outcome (cAPO) versus non cAPO (n=237 pregnancies).

Survival analysis, log-rank (Mantel-Cox) test.

DISCUSSION

This was the largest and most comprehensive study of pregnancy outcomes in women after KT stratified per prepregnancy eGFR-CKD-category. The study has three major findings. First, overall obstetric outcomes in KT-recipients are positive with 93% live birth rate >20 weeks of gestation, mean gestational age 35.6 weeks and mean birth weight 2383 (SD 885) gram. Second, this study shows that pregnancy outcomes in women with poor prepregnancy kidney function are also relatively good. Also, prepregnancy eGFR, mid-term percentage SCr dip and mid-term MAP dip are independent predictors for adverse pregnancy outcomes. Third, the occurrence of adverse pregnancy outcomes identifies patients at high risk of graft loss after pregnancy- although it is no predictor for graft loss on its own.

Because of low maternal adverse event rates, a combined adverse outcome was established. The choice of outcome parameters was based on clinical relevance and common use regarding maternal and neonatal morbidity and mortality.[30,31,48-50] The risk factors we found – prepregnancy eGFR, MAP-drop and SCr-dip - seem physiologically intuitive but are now shown to be statistically significantly related to adverse outcomes. By monitoring blood pressure and SCr values early in- and during pregnancy, adverse outcomes can be predicted. Thereby, surveillance can be intensified, e.g. additional ultrasounds can be organised and/or medication can be adjusted and pregnancy might be prolonged.

Despite the fact that pregnancies after KT have become more common, the risk of adverse pregnancy outcomes has not become lower. This reflects the more advanced comorbid conditions under which pregnancies take place. The high incidences of the composite adverse outcome set aside, for women after KT who wish to conceive, the numbers seem encouraging with 93% live birth rate >20 weeks gestation and 86% 'take home baby' rate.

Comparison with other studies

Fetal and maternal outcomes of our total study group were largely consistent with previous studies on pregnancy after KT.[8,12]

However, when comparing KT-recipients and women with CKD, KT-recipients showed higher incidences of preterm birth, low birth weight and/or SGA.[7,51] This difference might be explained by CKD and KT being different entities, with different renal impairment mechanisms and different therapies. Often no distinction is made in underlying kidney disease while this matters for the outcome.[52] Furthermore, physiological SCr-rise in third trimester[53] might be understood as a process mimicking preeclampsia, in absence of a proper definition for women with CKD. This

could explain variation in clinician's threshold for iatrogenic preterm delivery. With 288 pregnancies, this is the first and largest study on pregnancy outcomes after KT stratified per prepregnancy eGFR-CKD-category, compared to a recent study in CKD stage 3-5 including 43 KT-recipients without showing separate outcomes for KT-recipients.[7]

The association between mid-term percentage SCr dip, mid-term MAP dip and the composite adverse pregnancy outcome reflects the graft's reserve capacity and the ability of vascular adaptation to the pregnancy. These predictive factors have not been described in the KT population on this scale before, but have also been described in the healthy population and the pregnant CKD-population.[7,40,41,53-56]

Our results of 23% death censored graft loss post-pregnancy with a median follow-up of 7 years (IQR 13) match the findings of a recent meta-analysis.[57] When corrected for prepregnancy eGFR – a known predictor for graft survival-[34,58-60] the effect of adverse pregnancy outcomes on graft loss was no longer significant. Unmeasured confounders could not be taken into account. Although the intuitive relationship between adverse pregnancy outcomes and graft loss can be seen, it does not prove to be a predictor for graft loss on its own.

Koenjer et al investigated the influence of calcineurin inhibitors (CNI) on pregnancy outcomes and found no significant adverse outcomes.[37] However, there is a time effect leading to bias because of introduction of CNIs only in the nineties and mostly women with good kidney function getting pregnant at that time. In our prediction analysis no significant effect of transplant-era or decennium was found.

A survey in the Italian pregnant KT population suggested increased obstetric attention may had led to more interventions in women with growth-restricted babies, with more preterm birth and less SGA after the year 2000.[61] A trend of higher incidence of preterm birth was also seen in our study, without a decrease in SGA. This is likely explained by the more comorbid circumstances under which pregnancies took place in the Netherlands over time. However, in both studies, lacking information on ultrasounds or dopplers makes the establishment of true FGR versus SGA complex.

Strengths and limitations

The novelty and major strength of this study is that pregnancy outcomes after KT are shown on a large scale, stratified per prepregnancy eGFR-CKD-category including women with poor kidney function. The unique nationwide collaboration provided a large, unselected cohort of consecutive pregnancies after KT with a long-term follow up. In contrast to previous studies on pregnancy after KT, missing data were shown transparently and were handled according to up-to-date standards by multiple im-

putation for prediction analysis.[62-64] With limited bias, our results are generalisable for most settings.

This study has several limitations. First, due to the large time span for inclusion and its retrospective nature, obstetric and transplant policies have changed over time. When interpreting the results of our study, a time effect should be taken into account with an over-representation of women with good kidney function in earlier time periods. Nevertheless, no significant effects of decade or 'transplant'-era were seen in prediction analysis. Also, definitions for outcomes could differ over time, with a lacking proper definition for superimposed preeclampsia exists in women with CKD.

Second, although much effort was undertaken to carefully address missing values, missing data is a limitation of our study. Bias was introduced by the exclusion of pregnancies missing on the composite adverse pregnancy outcome from prediction analysis. However, multiple imputation of missing predictor values did not suggest an imbalance in their distribution as compared to observed values.

Third, unfortunately no further analyses could be performed on antihypertensive treatment because of missing data and poor validity of registered medication. Likewise, the influence of prepregnancy use of angiotensin-converting enzyme inhibitors or proteinuria levels on pregnancy outcomes could not be investigated.

Finally, clinical reasons underlying premature iatrogenic birth could not be analysed. From our experiences (superimposed) preeclampsia, renal function decline and/or (suspected) fetal growth restriction are the most common indications for early delivery.

Implications

Although pregnancy after KT in the Netherlands remains high risk, the majority of pregnancies are succesfull. Pregnancy outcomes sorted per prepregnancy eGFR-CKD-category are helpful for individualised prepregnancy counseling. Independent predictors for adverse outcomes such as prepregnancy eGFR and (the absence of) mid-term SCr and blood pressure drop help identifying high risk pregnancies. This can help the clinician in optimising frequency of consultations during pregnancy for better policy making.

Future research

The limitations of our study emphasize the need for prospective follow-up studies on pregnancy after KT. To this end, the PARTOUT-network continues to gather data prospectively. A European network is being established to gather more information

on pregnancy after KT on an even larger scale. As such, health care for women with a wish to conceive after KT can be improved.

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REFERENCES

1. Murray JE, Reid DE, Harrison JH, et al. Successful pregnancies after human renal transplantation. *N Engl J Med*. Aug 15 1963;269:341-3.
2. Saliem S, Patenaude V, Abenhaim HA. Pregnancy outcomes among renal transplant recipients and patients with end-stage renal disease on dialysis. *J Perinat Med*. Apr 2016;44(3):321-7.
3. Hamilton BE, Martin JA, Ostermann MJK, et al. *Births: Provisional Data for 2018* Vol. 004. Statistics DoV; 2018. May 2018. https://www.cdc.gov/nchs/data/vsrr/report004.pdf
4. Gill JS, Zalunardo N, Rose C, et al. The pregnancy rate and live birth rate in kidney transplant recipients. *Am J Transplant*. Jul 2009;9(7):1541-9.
5. Wyld ML, Clayton PA, Jesudason S, et al. Pregnancy outcomes for kidney transplant recipients. *Am J Transplant*. Dec 2013;13(12):3173-82.
6. Davison JM, Bailey DJ. Pregnancy following renal transplantation. *J Obstet Gynaecol Res*. Aug 2003;29(4):227-33.
7. Wiles K, Webster P, Seed PT, et al. The impact of chronic kidney disease Stages 3-5 on pregnancy outcomes. *Nephrol Dial Transplant*. Dec 12 2020;
8. Bramham K, Nelson-Piercy C, Gao H, et al. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol*. Feb 2013;8(2):290-8. doi:10.2215/cjn.06170612
9. Stoumpos S, McNeill SH, Gorrie M, et al. Obstetric and long-term kidney outcomes in renal transplant recipients: a 40-yr single-center study. *Clin Transplant*. Jun 2016;30(6):673-81. doi:10.1111/ctr.12732
10. Mohammadi FA, Borg M, Gulyani A, et al. Pregnancy outcomes and impact of pregnancy on graft function in women after kidney transplantation. *Clin Transplant*. Oct 2017;31(10)doi:10.1111/ctr.13089
11. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int*. Jan 2014;85(1):49-61. doi:10.1038/ki.2013.444
12. Shah S, Venkatesan RL, Gupta A, et al. Pregnancy outcomes in women with kidney transplant: Metaanalysis and systematic review. *BMC Nephrol*. Jan 23 2019;20(1):24.
13. Hack KE, Derks JB, Elias SG, et al. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. *Bjog*. Jan 2008;115(1):58-67. doi:10.1111/j.1471-0528.2007.01556.x
14. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 50, January 2003. *Obstet Gynecol*. Jan 2004;103(1):203-16.
15. *OpenClinica* Version 3.1. 2019.
16. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis*. Apr 2010;55(4):622-7. doi:10.1053/j.ajkd.2010.02.337
17. Hoftiezer L, Hukkelhoven CW, Hogeveen M, et al. Defining small-for-gestational-age: prescriptive versus descriptive birthweight standards. *Eur J Pediatr*. Aug 2016;175(8):1047-57.
18. Bakketeig LS, Bergsjø P. Perinatal Epidemiology. In: Heggenhougen HK, ed. *International Encyclopedia of Public Health*. Academic Press; 2008:45-53.

19. Lane D, Lawson A, Burns A, et al. Nonadherence in Hypertension: How to Develop and Implement Chemical Adherence Testing. *Hypertension*. Jan 2022;79(1):12-23. doi:10.1161/hypertensionaha.121.17596
20. Blaschke TF, Osterberg L, Vrijens B, et al. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol*. 2012;52:275-301. doi:10.1146/annurev-pharmtox-011711-113247
21. Meddings J, Kerr EA, Heisler M, et al. Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss. *BMC Health Serv Res*. Aug 21 2012;12:270. doi:10.1186/1472-6963-12-270
22. Webster K, Fishburn S, Maresh M, et al. Guideline C. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. *Bmj*. Sep 9 2019;366:l5119.
23. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. Apr 1988;158(4):892-8.
24. Grindheim G, Estensen ME, Langesaeter E, et al. Changes in blood pressure during healthy pregnancy: a longitudinal cohort study. *J Hypertens*. Feb 2012;30(2):342-50.
25. Clapp JF, 3rd, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol*. Dec 1 1997;80(11):1469-73.
26. van Oppen AC, van der Tweel I, Alsbach GP, et al. A longitudinal study of maternal hemodynamics during normal pregnancy. *Obstet Gynecol*. Jul 1996;88(1):40-6.
27. Ayala DE, Hermida RC, Mojón A, et al. Blood pressure variability during gestation in healthy and complicated pregnancies. *Hypertension*. Sep 1997;30(3 Pt 2):611-8.
28. Lopes van Balen VA, Spaan JJ, Ghossein C, et al. Early pregnancy circulatory adaptation and recurrent hypertensive disease: an explorative study. *Reprod Sci*. Sep 2013;20(9):1069-74.
29. Sturgiss SN, Dunlop W, Davison JM. Renal haemodynamics and tubular function in human pregnancy. *Baillieres Clin Obstet Gynaecol*. Jun 1994;8(2):209-34.
30. WHO. Preterm Birth Fact Sheet WHO. Updated 19/02/2018. 2020. https://www.who.int/news-room/fact-sheets/detail/preterm-birth. *Last accessed 03-05-2022*.
31. WHO. Low Birth Weight Indicator Metadata Registry Details. WHO. 2020. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/76. *Last accessed 03-05-2022*.
32. LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. Dec 2 2014;161(11):819-26. doi:10.7326/m14-1884
33. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med*. Jan 29 2015;372(5):407-17. doi:10.1056/NEJMoa1404595
34. van Buren MC, Gosselink M, Groen H, et al. Effect of Pregnancy on EGFR After Kidney Transplantation: a National Cohort Study. *Transplantation*. Aug 27 2021;doi:10.1097/tp.0000000000003932
35. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J Am Soc Nephrol*. Nov 2009;20(11):2433-40. doi:ASN.2008121241 [pii]10.1681/ASN.2008121241
36. Cabiddu G, Spotti D, Gernone G, et al. A best-practice position statement on pregnancy after kidney transplantation: focusing on the unsolved questions. The Kidney and Pregnancy Study Group of the Italian Society of Nephrology. *J Nephrol*. Oct 2018;31(5):665-681. doi:10.1007/s40620-018-0499-x

37. Koenjer LM, Meinderts JR, van der Heijden OWH, et al. Comparison of pregnancy outcomes in Dutch kidney recipients with and without calcineurin inhibitor exposure: a retrospective study. *Transpl Int*. Dec 2021;34(12):2669-2679. doi:10.1111/tri.14156

38. Sullivan TR, Lee KJ, Ryan P, et al. Multiple imputation for handling missing outcome data when estimating the relative risk. *BMC Med Res Methodol*. Sep 6 2017;17(1):134.

39. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant*. Nov 2011;11(11):2388-404.

40. Macdonald-Wallis C, Tilling K, Fraser A, et al. Associations of blood pressure change in pregnancy with fetal growth and gestational age at delivery: findings from a prospective cohort. *Hypertension*. Jul 2014;64(1):36-44.

41. Park S, Lee SM, Park JS, et al. Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of Gestational Hyperfiltration. *Clin J Am Soc Nephrol*. Jul 7 2017;12(7):1048-1056.

42. Gaston RS, Fieberg A, Hunsicker L, et al. Late graft failure after kidney transplantation as the consequence of late versus early events. *Am J Transplant*. May 2018;18(5):1158-1167.

43. Rose C, Gill J, Gill JS. Association of Kidney Transplantation with Survival in Patients with Long Dialysis Exposure. *Clin J Am Soc Nephrol*. Dec 7 2017;12(12):2024-2031.

44. Bailey P, Edwards A, Courtney AE. Living kidney donation. *Bmj*. Sep 14 2016;354:i4746.

45. Papalois VE, Moss A, Gillingham KJ, et al. Pre-emptive transplants for patients with renal failure: an argument against waiting until dialysis. *Transplantation*. Aug 27 2000;70(4):625-31.

46. Mange KC, Feldman HI, Joffe MM, et al. Blood pressure and the survival of renal allografts from living donors. *J Am Soc Nephrol*. Jan 2004;15(1):187-93.

47. Foroutan F, Friesen EL, Clark KE, et al. Risk Factors for 1-Year Graft Loss After Kidney Transplantation: Systematic Review and Meta-Analysis. *Clin J Am Soc Nephrol*. Nov 7 2019;14(11):1642-1650.

48. Cutland CL, Lackritz EM, Mallett-Moore T, et al. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. *Vaccine*. 2017/12// 2017;35(48 Pt A):6492-6500. doi:10.1016/j.vaccine.2017.01.049

49. Badshah S, Mason L, McKelvie K, et al. Risk factors for low birthweight in the public-hospitals at Peshawar, NWFP-Pakistan. *BMC public health*. 2008;8:197. doi:10.1186/1471-2458-8-197.

50. Watkins WJ, Kotecha SJ, Kotecha S. All-Cause Mortality of Low Birthweight Infants in Infancy, Childhood, and Adolescence: Population Study of England and Wales. *PLoS medicine*. 2016;13(5):e1002018. doi:10.1371/journal.pmed.1002018

51. Piccoli GB, Cabiddu G, Attini R, et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. *J Am Soc Nephrol*. Aug 2015;26(8):2011-22.

52. Fitzpatrick A, Venugopal K, Scheil W, et al. The Spectrum of Adverse Pregnancy Outcomes Based on Kidney Disease Diagnoses: A 20-Year Population Study. *Am J Nephrol*. 2019;49(5):400-409. doi:10.1159/000499965

53. Lopes van Balen VA, van Gansewinkel TAG, de Haas S, et al. Maternal kidney function during pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. Sep 2019;54(3):297-307.

54. Page EW, Christianson R. The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy. *Am J Obstet Gynecol*. Jul 15 1976;125(6):740-6.

55. Williams D, Davison J. Chronic kidney disease in pregnancy. *Bmj*. Jan 26 2008;336(7637):211-5.

56. Gaillard R, Bakker R, Willemsen SP, et al. Blood pressure tracking during pregnancy and the risk of gestational hypertensive disorders: the Generation R Study. *Eur Heart J*. Dec 2011;32(24):3088-97.
57. van Buren MC, Schellekens A, Groenhof TKJ, et al. Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis. *Transplantation*. Aug 2020;104(8):1675-1685.
58. Thompson BC, Kingdon EJ, Tuck SM, et al. Pregnancy in renal transplant recipients: the Royal Free Hospital experience. *Qjm*. Nov 2003;96(11):837-44. doi:10.1093/qjmed/hcg142
59. Kato M, Hattori R, Kinukawa T, et al. Correlation between treated hypertension in prepregnancy and transplanted kidney function deterioration during pregnancy even if within pregnancy permission criteria. *Transplant Proc*. Apr 2012;44(3):635-7. doi:10.1016/j.transproceed.2011.11.038
60. Aivazoglou L, Sass N, Silva HT, et al. Pregnancy after renal transplantation: an evaluation of the graft function. *Eur J Obstet Gynecol Reprod Biol*. Apr 2011;155(2):129-31. doi:10.1016/j.ejogrb.2010.11.020
61. Piccoli GB, Cabiddu G, Attini R, et al. Pregnancy outcomes after kidney graft in Italy: are the changes over time the result of different therapies or of different policies? A nationwide survey (1978-2013). *Nephrol Dial Transplant*. Nov 2016;31(11):1957-1965. doi:10.1093/ndt/gfw232
62. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj*. Jun 29 2009;338:b2393.
63. Buuren van S. *Flexible Imputation of Missing Data* vol 2. Chapman & Hall/CRC; 2018.
64. Moons KGM, Wolff RF, Riley RD, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. *Ann Intern Med*. Jan 1 2019;170(1):W1-W33.

SUPPLEMENTARY MATERIAL

Supplementary File

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Table S1. Baseline characteristics of twin pregnancies

Number of pregnancies	13
Cause of kidney failure Glomerulonephritis Interstitial Other	4/11 (36%) 2/11 (18%) 5/11 (45%)
History of multiple transplantations before pregnancy	3/12 (25%)
Type of transplant, Living donor	6/13 (46%)
Pregnancy before KT	2/12 (17%)
History of preterm birth before KT	0
History of pre-eclampsia before KT	0
Median transplant conception interval (TCI), years (IQR)	5 (3)
Caucasian race	9/9 (100%)
Median age at pregnancy, years (IQR)	30 (7)
Median BMI at pregnancy (IQR)	23 (7)
Chronic hypertension	5/9 (56%)
Prepregnancy serum creatinine, µmol/L	112 (58)

Data are presented as mean (SD) and n (%) unless stated otherwise. Not all baseline characteristics were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases are described here: *Age at pregnancy: n = 10 . TCI: n = 10; prepregnancy serum creatinine: n = 10; BMI at pregnancy: n = 5.* BMI = body mass index.

Table S2. Twin pregnancy outcomes

Neonatal outcomes		
Gestational age, days	208 (72)	
Gestational age, weeks	29.7	
Preterm birth		
<37 weeks	9/10 (90%)	
<34 weeks	5/10 (50%)	
<28 weeks	3/10 (30%)	
	Child A	***Child B***
Birth weight, gram (SD)	1662 (735)	2046 (386)
<2500 gram	9/10 (90%)	8/8 (100%)
<1500 gram	2/10 (20%)	1/8 (13%)
Percentile corrected for gestational age (IQR)	4 (9)	7 (44)
Small for gestation age		

Table S2. Twin pregnancy outcomes *Continued*

Neonatal outcomes		
<p10	4/7 (57%)	4/6 (67%)
<p5	4/7 (57%)	2/6 (33%)
Apgar ≤5, 5 minutes after birth	0	0
NICU admission	4/9 (44%)	4/8 (50%)
Stillbirth	1/11 (9%)	1/10 (10%)
Neonatal mortality (in first 7 days of life)	0	0
Maternal outcomes		
Gestational hypertension	3/9 (33%)	
Pre-eclampsia	3/9 (33%)	
Rejection therapy during pregnancy	0	

Data are presented as mean (SD) and n (%) unless stated otherwise. Not all baseline characteristics were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases are described here: *Gestational age: n = 10; Birthweight: n = 18; Percentile corrected for gestational age: n = 13*

Table S3. Use of antihypertensive medication during pregnancy.

Variable	**All pregnancies** *N = 231*	**eGFR** ≥90 ml/min/1.73m² *N = 15*	**eGFR 89-60** ml/min/1.73m² *N = 80*	**eGFR 56-45**ml/min/1.73m² *N = 63*	**eGFR 44-30** ml/min/1.73m² *N = 42*	**eGFR<30** ml/min/1.73m² *N = 9*
Use of antihypertensive medication during pregnancy	163/231 (71%)	6/15 (40%)	52/80 (65%)	48/63 (76%)	34/42 (81%)	8/9 (89%)
Use of antihypertensive medication 1st trimester	132/163 (81%)	3/6 (50%)	39/52 (75%)	37/48 (77%)	31/34 (91%)	8/8 (100%)
Specific treatment 1st trimester						
Methyldopa	44/156 (28%)	2/6 (33%)	15/48 (31%)	14/46 (30%)	6/33 (18%)	3/8 (38%)
Labetalol	44/156 (28%)	0 (0%)	14/48 (29%)	13/46 (28%)	10/33 (30%)	0 (0%)
Nifedipine	15/156 (9%)	0 (0%)	4/48 (8%)	3/46 (6,5%)	7/33 (21%)	1/8 (12,5%)
Other antihypertensiva	74/156 (47%)	1/6 (17%)	16/48 (33%)	18/46 (39%)	29/33 (88%)	8/8 (100%)
Triple (or more) therapy	5/156 (3%)	0 (0%)	1/48 (2%)	1/46 (2%)	2/33 (6%)	1/8 (12,5%)
Use of antihypertensive medication 2nd trimester	138/163 (85%)	3/6 (50%)	41/52 (79%)	40/48 (83%)	32/34 (94%)	8/8 (100%)
Specific treatment 2nd trimester						
Methyldopa	55/157 (35%)	2/6 (33%)	16/49 (33%)	18/45 (40%)	8/34 (24%)	5/8 (63%)
Labetalol	45/157 (29%)	0 (0%)	13/49 (27%)	13/45 (29%)	12/34 (35%)	0 (0%)
Nifedipine	26/157 (17%)	0 (0%)	5/49 (10%)	7/45 (16%)	11/34 (32%)	2/8 (25%)
Other antihypertensiva	75/157 (48%)	1/6 (17%)	16/49 (33%)	17/45 (38%)	30/34 (88%)	8/8 (100%)
Triple (or more) therapy	9/157 (6%)	0	0	1/45 (2%)	5/34 (15%)	2/8 (25%)
Use of antihypertensive medication 3rd trimester	151/153 (99%)	6/6 (100%)	47/48 (98%)	44/45 (98%)	33/33 (100%)	8/8 (100%)

Table S3. Use of antihypertensive medication during pregnancy. *Continued*

Variable	All pregnancies *N = 231*	eGFR ≥90 ml/min/1.73m² *N = 15*	eGFR 89-60 ml/min/1.73m² *N = 80*	eGFR 56-45ml/min/1.73m² *N = 63*	eGFR 44-30 ml/min/1.73m² *N = 42*	eGFR<30 ml/min/1.73m² *N = 9*
Specific treatment 3rd trimester						
Methyldopa	67/152 (44%)	4/6 (67%)	22/48 (46%)	24/45 (53%)	8/33 (24%)	4/7 (57%)
Labetalol	54/152 (36%)	0 (0%)	15/48 (31%)	18/45 (40%)	13/33 (39%)	1/7 (14%)
Nifedipine	40/152 (26%)	0 (0%)	8/48 (17%)	17/45 (38%)	13/33 (39%)	2/ (29%)
Other antihypertensiva	77/152 (51%)	2/6 (33%)	17/48 (35%)	18/45 (40%)	30/33 (91%)	7/7 (100%)
Triple (or more) therapy	20/152 (13%)	0 (0%)	1/48 (2%)	10/45 (22%)	6/33 (18%)	2/7 (29%)

Not for all pregnancies with antihypertensive treatment specific medication was known. Incidences are shown numerator/denominator (%). Missing values regarding use of antihypertensive medication during pregnancy: All pregnancies: n = 58 (20%). eGFR-categories: CKD-stage 1 n = 8, CKD-stage 2 n = 24, CKD-stage 3a n = 9, CKD-stage 3b n = 2, CKD-stage 4&5 n = 1. Use of antihypertensive medication and specific treatment during trimesters is given for pregnancies using antihypertensive treatment (n=163).

Table S4. Use of immunosuppressive medication before and during pregnancy.

Variable	All pregnancies *N = 278*	eGFR ≥90 ml/min/1.73m² *N = 21*	eGFR 89-60 ml/min/1.73m² *N = 102*	eGFR 56-45 ml/min/1.73m² N = 72	eGFR 44-30 ml/min/1.73m² N = 44	eGFR<30 ml/min/1.73m² *N = 10*
Use of immune suppressive medication during pregnancy	278/278 (100%)	21/21 (100%)	102/102 (100%)	72/72 (100%)	44/44 (100%)	10/10 (100%)
Use of immune suppressive medication during 1st trimester	276/276 (100%)	21/21 (100%)	102/102 (100%)	72/72 (100%)	44/44 (100%)	10/10 (100%)
Specific treatment 1st trimester						
Prednison	250/275 (91%)	20/21 (95%)	92/100 (92%)	67/71 (94%)	36/44 (82%)	10/10 (100%)
Azathioprine	195/275 (71%)	19/21 (91%)	78/100 (78%)	49/71 (69%)	26/44 (59%)	4/10 (40%)
Calcineurin Inhibitor	141/275 (51%)	6/21 (29%)	42/100 (42%)	39/71 (55%)	32/44 (73%)	6/10 (60%)
Tacrolimus	79/275 (29%)	3/21 (14%)	25/100 (25%)	25/71 (35%)	19/44 (43%)	2/10 (20%)
Ciclosporine	62/275 (23%)	3/21 (14%)	17/100 (17%)	14/71 (20%)	13/44 (30%)	4/10 (40%)
Mycophenolate mofetil	3/275 (1%)	0%	1/100 (1%)	2/71 (3%)	0%	0%
Other	2/275 (1%)	0%	2/100 (2%)	0%	0%	0%
Use of immune suppressive medication during 2nd trimester	276/276 (100%)	21/21 (100%)	101/101 (100%)	71/71 (100%)	44/44 (100%)	10/10 (100%)
Specific treatment 2nd trimester						
Prednison	250/275 (87%)	20/21 (95%)	92/100 (92%)	67/71 (94%)	36/44 (82%)	10/10 (100%)
Azathioprine	195/275 (71%)	19/21 (91%)	78/100 (78%)	49/71 (69%)	26/44 (59%)	4/10 (40%)
CNI	139/275 (48%)	6/21 (29%)	42/100 (42%)	37/71 (52%)	32/44 (73%)	6/10 (60%)
Tacrolimus	78/275 (28%)	3/21 (14,3%)	25/100 (25%)	24/71 (34%)	19/44 (43%)	2/10 (20%)
Ciclosporine	61/275 (21%)	3/21 (14,3%)	17/100 (17%)	13/71 (18%)	13/44 (30%)	4/10 (40%)

Table S4. Use of immunosuppressive medication before and during pregnancy. *Continued*

Variable	All pregnancies *N = 278*	eGFR ≥90 ml/min/1.73m² *N = 21*	eGFR 89-60 ml/min/1.73m² *N = 102*	eGFR 56-45 ml/min/1.73m² N = 72	eGFR 44-30 ml/min/1.73m² N = 44	eGFR<30 ml/min/1.73m² *N = 10*
Mycophenolate mofetil	0%	0%	0%	0%	0%	0%
Other	3/275 (1%)	0%	2/100 (2%)	1/71 (1%)	0%	0%
Use of immune suppressive medication during 3rd trimester	271/271 (100%)	21/21 (100%)	100/100 (100%)	70/70 (100%)	44/44 (100%)	9/9 (100%)
Specific treatment 3rd trimester						
Prednison	245/269 (91%)	20/21 (95%)	91/99 (92%)	66/70 (94%)	36/44 (82%)	8/8 (100%)
Azathioprine	195/269 (73%)	19/21 (91%)	78/99 (79%)	50/70 (71%)	27/44 (61%)	4/8 (50%)
CNI	139/269 (52%)	6/21 (29%)	42/99 (42%)	39/70 (56%)	32/44 (73%)	6/8 (75%)
Tacrolimus	75/269 (28%)	3/21 (14%)	24/99 (24%)	24/70 (34%)	19/44 (43%)	2/8 (25%)
Ciclosporine	64/269 (24%)	3/21 (14%)	18/99 (18%)	15/70 (21%)	13/44 (30%)	4/8 (50%)
Mycophenolate mofetil	0 (0%)	0%	0%	0%	0%	0%
Other	2/269 (1%)	0%	2/99 (2%)	0%	0%	0%

Use of immune suppressive medication and specific treatment during trimesters is given for pregnancies using immune suppressive treatment (n=278). Not for all pregnancies with immune suppressive medication, specific medication was known. Incidences are shown numerator/denominator (%). Missing values use of immune suppressive medication during pregnancy: All pregnancies: n =12. eGFR-categories: CKD-stage 1 n = 2 , CKD-stage 2 n = 2, CKD-stage 3a n = 2 , CKD-stage 3b n = 2, CKD-stage 4&5 n = 0.

Table S5. Baseline characteristics stratified per decennium.

	1980-1990	1990-2000	2000-2010	2010-2017
Number of pregnancies	53/286 (19%)	62/286 (22%)	77/286 (27%)	94/286 (33%)
Cause of kidney failure				
Glomerulonephritis	19/47 (40%)	27/60 (45%)	24/70 (34%)	27/81 (33%)
Interstitial	10/47 (21%)	11/60 (18%)	15/70 (21%)	7/81 (9%)
Diabetes	0	1/60 (2%)	0	5/81 (6%)
Auto-immune	2/47 (4%)	3/60 (5%)	3/70 (4%)	3/81 (4%)
Other	16/47 (34%)	18/60 (30%)	28/70 (40%)	37/81 (46%)
History of multiple transplantations before pregnancy	12/53 (23%)	18/62 (29%)	12/77 (16%)	18/94 (19%)
Type of transplant, Living donor*	2/45 (4%)	10/62 (16%)	34/74 (46%)	65/89 (73%)
Pregnancy before KT	12/48 (25%)	6/62 (10%)	10/77 (13%)	20/91 (22%)
History of preterm birth before KT	1/48 (2%)	2/62 (3%)	5/77 (6%)	10/91 (11%)
History of pre-eclampsia before KT	1/48 (2%)	0	2/77 (3%)	7/91 (8%)
Median transplant conception interval (TCI), years (IQR)	6 (7)	5 (6)	7 (6)	5 (6)
Caucasian race	32/53 (60%)	33/62 (53%)	50/77 (65%)	57/94 (61%)
Median age at pregnancy, years (IQR)	30 (4)	32 (6)	33 (6)	32 (5)
Median BMI at pregnancy (IQR)	23 (3)	24 (5)	24 (5)	24 (6)
Chronic hypertension	16/36 (44%)	30/51 (59%)	44/74 (59%)	56/88 (64%)
Prepregnancy eGFR, ml/min/1.73m²	69 (18)	63 (26)	62 (21)	58 (19)

Data are presented as mean (SD) an n (%) unless stated otherwise. Not all baseline characteristics were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases is described here: *TCI n = 268, Age at pregnancy n = 274, BMI at pregnancy n = 180.* BMI = Body Mass Index. eGFR calculated with the CKD-EPI method. *Type of transplant, living donor differed significantly between decennia (p = <0.001).

Table S6. Pregnancy outcomes stratified per decennium.

	1980-1990	1990-2000	2000-2010	2010-2017
Neonatal outcomes				
Gestational age, days	254 (24)	250 (29)	252 (30)	243 (34)
Gestational age, weeks	36.3	35.7	36.0	34.7
Preterm birth				
<37 weeks	20/45 (44%)	25/56 (45%)	33/74 (45%)	54/90 (60%)
<34 weeks	6/45 (13%)	15/56 (27%)	16/74 (22%)	27/90 (30%)
<28 weeks	1/45 (2%)	2/56 (4%)	6/74 (8%)	9/90 (10%)
Birth weight, gram (SD)	2630 (883)	2205 (912)	2536 (888)	2245 (832)
<2500 gram	17/43 (40%)	30/54 (56%)	30/74 (41%)	52/90 (58%)
<1500 gram	6/43 (14%)	11/54 (20%)	8/74 (11%)	16/90 (18%)
Percentile corrected for gestational age (IQR)	32 (60)	8 (33)	21 (56)	11 (30)
Small for gestation age				
<p10	13/37 (35%)	28/51 (55%)	26/71 (37%)	35/83 (42%)
<p5	8/37 (22%)	21/51 (41%)	18/71 (25%)	17/83 (20%)
Apgar ≤5, 5 minutes after birth	0	6/35 (17%)	5/56 (9%)	4/81 (5%)
NICU admission	3/15 (20%)	6/41 (15%)	7/62 (11%)	12/83 (14%)
Stillbirth	3/51 (6%)	5/59 (8%)	5/77 (6%)	6/94 (6%)
Neonatal mortality (in first 7 days of life)	2/39 (5%)	3/55 (5%)	2/71 (3%)	1/88 (1%)
Maternal outcomes				
Gestational hypertension	16/28 (57%)	26/49 (53%)	37/72 (51%)	46/84 (55%)
Pre-eclampsia	8/31 (26%)	13/48 (27%)	25/67 (37%)	35/89 (39%)
Rejection therapy during pregnancy	0	0	2/70 (3%)	1/82 (1%)
Use of calcineurin inhibitor during pregnancy	3/48 (6%)	33/57 (58%)	38/75 (51%)	67/93 (72%)

Data are presented as mean (SD) an n (%) unless stated otherwise. Not all pregnancy outcomes were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases is described here: *gestational age n = 265, birth weight n = 261, percentile corrected for gestational age n = 242.*

Table S7. Baseline characteristics stratified per use of CNI (CyA and tacrolimus)

	CNI Yes	CNI No
Number of pregnancies	143/275 (52%)	132/275 (48%)
Cause of kidney failure		
Glomerulonephritis	43/128 (34%)	51/117 (44%)
Interstitial	24/128 (19%)	15/117 (13%)
Diabetes	5/128 (4%)	0
Auto-immune	4/128 (3%)	7/117 (6%)
Other	52/128 (41%)	45/117 (38%)
History of multiple transplantations before pregnancy	34/143 (25%)	23/132 (17%)
Type of transplant, Living donor	63/134 (47%)	46/125 (35%)
Pregnancy before KT	28/140 (20%)	18/127 (14%)
History of preterm birth before KT	13/28 (46%)	5/18 (28%)
History of pre-eclampsia before KT	7/28 (25%)	3/18 (17%)
Median transplant conception interval (TCI), years (IQR)	4 (5)	7 (7)
Caucasian race	83/102 (81%)	86/99 (87%)
Median age at pregnancy, years (IQR)	32 (5)	31 (6)
Median BMI at pregnancy (IQR)	24 (6)	23 (4)
Chronic hypertension	81/131 (62%)	66/117 (56%)
Prepregnancy eGFR, ml/min/1.73m^2	57 (20)	66 (21)

Data are presented as mean (SD) an n (%) unless stated otherwise. Not all baseline characteristics were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases is described here: *TCI n = 261, Age at pregnancy n = 267, BMI at pregnancy n = 179. Prepregnancy eGFR n = 246.* BMI = Body Mass Index. eGFR calculated with the CKD-EPI method.

Table S8. Pregnancy outcomes stratified per use of CNI (CyA and tacrolimus)

	CNI Yes	CNI No
Neonatal outcomes		
Gestational age, days	247 (32)	251 (28)
Gestational age, weeks	35.3	35.9
Preterm birth		
<37 weeks	70/133 (53%)	58/124 (47%)
<34 weeks	36/133 (27%)	26/124 (21%)
<28 weeks	10/133 (8%)	8/124 (7%)
Birth weight, gram (SD)	2318 (895)	2486 (835)
<2500 gram*	74/135 (55%)	49/118 (42%)
<1500 gram	22/135 (16%)	16/118 (14%)
Percentile corrected for gestational age (IQR)	12 (40)	21 (51)
Small for gestation age		
<p10	55/125 (44%)	40/111 (36%)
<p5	35/125 (28%)	24/111 (22%)
Apgar ≤5, 5 minutes after birth	9/104 (9%)	5/72 (7%)
NICU admission	15/113 (13%)	13/84 (16%)
Stillbirth	11/142 (8%)	6/129 (5%)
Neonatal mortality (in first 7 days of life)	5/134 (4%)	3/115 (3%)
Maternal outcomes		
Gestational hypertension**	76/124 (61%)	47/105 (45%)
Pre-eclampsia	47/127 (37%)	31/103 (30%)
Rejection therapy during pregnancy	2/120 (2%)	0

Data are presented as mean (SD) an n (%) unless stated otherwise. Not all pregnancy outcomes were available for all pregnancies. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases is described here: *gestational age n = 257, birth weight n = 253, percentile corrected for gestational age n = 236. *p = 0.035. **p=0.012*

Table S9. cAPO frequencies

Outcome	Incidence (%, 95% CI)
Total composite outcome (*)	186/237 (78%, 68 to 91%)
Preterm birth <37 weeks*	137/233 (59%, 49 to 70%)
Birth weight < 2500 gram*	129/225 (57%, 48 to 68%)
Severe hypertension in third trimester*	44/175 (25%, 18 to 34%)
Increase serum creatinine > 15% during pregnancy*	45/198 (23%, 17 to 30%)

Table S10. Baseline characteristics of pregnancies for cAPO analysis, n = 237.

Variable	All pregnancies (N= 237)	With cAPO (N= 186)	Without cAPO (N= 51)
Preeclampsia in obstetric history, before KT	10 (4%)	8 (4%)	2 (4%)
Preterm birth in obstetric history, before KT	18 (8%)	15 (8%)	3 (6%)
History of multiple transplantations	54 (23%)	44 (24%)	10 (20%)
Median age at pregnancy (IQR)	31.5 (5.4)	31.6 (5.6)	31.4 (4.8)
Median transplant conception interval (IQR)	5 (8)	5 (8)	4 (7)
Prepregnancy eGFR, ml/min/1.73m²	62 (21)	59 (21)	67 (22)
Pre-existing hypertension	130/214 (61%)	102/168 (61%)	28/46 (61%)
SBP prior to conception, mmHg	124 (14)	124 (14)	125 (15)
DBP prior to conception, mmHg	79 (10)	79 (9)	79 (10)
Median BMI at pregnancy (IQR)	24.1 (5.0)	24.1 (4.8)	23.4 (6.0)
Caucasian race	147/177 (83%)	113/138 (82%)	34/39 (87%)
Cause of kidney failure			
Glomerulonephritis	94/212 (44%)	74/163 (45%)	20/49 (41%)
Interstitial	32/212 (15%)	24/163 (15%)	8 /49 (16%)
Other	86/212 (41%)	65/163 (40%)	21/43 (43%)
Type of transplant			
- Living donor	100/223 (42%)	77/173 (45%)	23/50 (46%)

Data are presented as mean (SD) and n (%) unless stated otherwise.

Table S11. Baseline characteristics of pregnancies with and without missing outcome data

Variable	Missing values of cAPO pregnancies, n = 51	Non-missing cAPO pregnancies, n = 237
Preeclampsia in obstetric history	0 / 51 (0%)	10/237 (4%)
Preterm birth in obstetric history	0 / 51 (0%)	18/237 (8%)
Multiple transplantations in history	7/51 (14%)	54/237 (23%)
Median age at pregnancy, years (IQR)	31 (4)	31,5 (5)
Median transplant conception interval, years (IQR)	5 (4)	5 (8)
Prepregnancy serum creatinine, µmol/L	96 (19)	120 (60)
Prepregnancy eGFR, ml/min/1.73m²	71 (17)	61 (21)
Chronic hypertension	17/37 (46%)	130/214 (61%)
SBP prior to conception, mmHg	124 (15)	124 (14)
DBP prior to conception, mmHg	82 (11)	79 (10)
Median BMI at pregnancy (IQR)	24 (6)	24 (5)
Caucasian race	27/30 (90%)	147/177 (83%)
Cause of kidney failure		
Glomerulonephritis	20/46 (26%)	94/212 (44%)
Interstitial	12/46 (44%)	32/212 (15%)
Other	14/46 (30%)	86/212 (41%)
Type of transplant		
- Living donor	11/48 (22%)	100/223 (45%)

Data are presented as mean (SD) and n (%) unless stated otherwise.

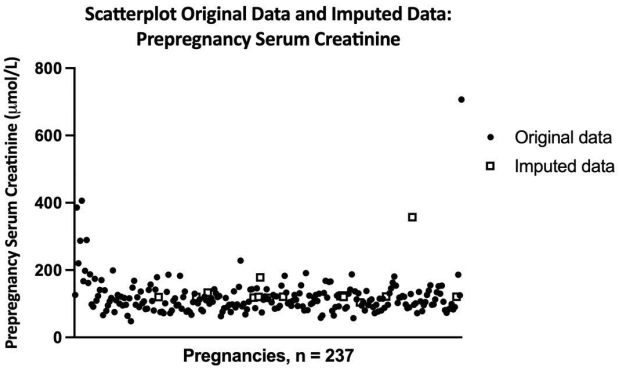
Table S12. Potential predictors before and after multiple imputation, n =237

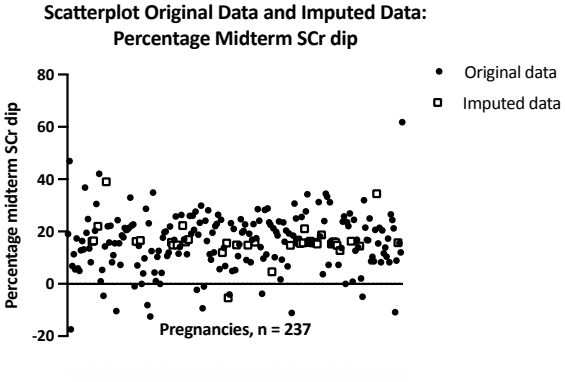
Variable	Before imputation	After imputation
Cause of kidney failure		
Glomerulonephritis	94 (44%)	105 (44%)
Interstitial	32 (15%)	36 (15%)
Other	86 (41%)	96 (41%)
Age at pregnancy	32 (5)	32 (5)
Median BMI at pregnancy (IQR)	24 (5)	25 (3)
NTx type		
Cadaver	123 (55%)	130 (55%)
Living	100 (45%)	107 (45%)
Median Transplant-conception interval (IQR)	5 (8)	5 (8)
Chronic hypertension	130 (61%)	143 (60%)

Table S12. Potential predictors before and after multiple imputation, n =237 *Continued*

Variable	Before imputation	After imputation
MAP drop 2nd trimester – prepregnancy, mmHg	1,56 (10,6)	1,69 (9,87)
SBP prior to pregnancy, mmHg	124 (14)	124 (13)
DBP prior to pregnancy, mmHg	79 (10)	79 (9)
MAP prior to pregnancy, mmHg	94 (10)	94 (9)
Prepregnancy serum creatinine, µmol/L	120 (60)	122 (61)
Prepregnancy eGFR, ml/min/1.73m²	61 (21)	60 (21)
Percentage SCr drop	16% (11%)	16% (10%)

Data are presented as mean (SD) and n (%) unless stated otherwise.





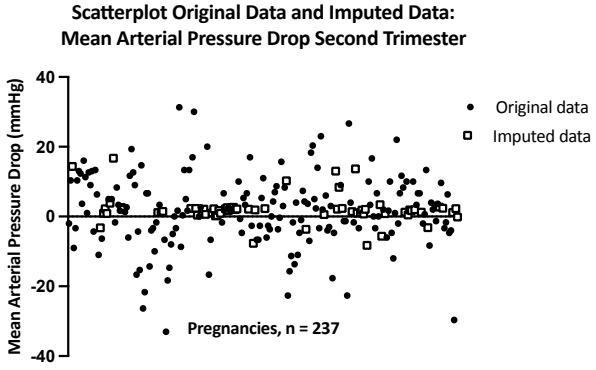


Figure S1. scatterplots for imputed predictors of APO

PART 2

Pre-pregnancy counseling in Kidney Transplant Recipients

Chapter 5

Essential Issues for Pregnancy Counseling in Kidney Transplant Women

Marleen C. van Buren, A. Titia Lely, Jacqueline van de Wetering

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Available data shows that successful pregnancy after kidney transplantation (KT) is possible, however higher rates of hypertension, proteinuria and deterioration of graft function have been reported, especially when pre-conceptional graft function is not optimal [1]. We would like to add some essential issues in counseling women who received a renal transplant and want to become pregnant.

At the Erasmus Medical Centre in Rotterdam, we performed a single centre retrospective study of pregnancies of KT recipients, who were transplanted between 1971 and 2016. Medical records of all women from 45 years or younger were assessed. We found 42 women who had one or more pregnancies with a gestational age longer than 6 months. Median follow up time after first delivery was 12,5 years (range 1-34 years). During follow up 5 (12%) of the women died 1 to 20 years after delivery (median 6 year). The median transplant-to-first delivery interval was 6,5 (range 1- 24) years. Graft loss was seen in 48% (20/42) after their first delivery, at a median time of 5,7 years (range 0 – 22 years) after delivery and a median time of 12,5 years (range 3 – 25 years) after KT. Graft survival after KT in this subgroup was better than graft survival of our whole KT population (2). For graft survival after delivery a Kaplan Meijer analysis was performed (figure 1).

In literature regarding pregnancy after KT there have been made several comparisons with the general population concerning live birth rate, preeclampsia, fetal growth restriction, preterm delivery, effect of pregnancy on rejection rates and graft survival [1,2]. Surprisingly, so far survival of the transplanted mother after she gave birth to a child has not been given a lot of attention. We show that 12% of these women did not get the chance to see their child reach adulthood, compared with the general Dutch population, where 3.9% of children loses one of their parents before they reach adulthood (4). We think this aspect is under-exposed in literature but of great importance in counseling. Of note is that these analyses are single centre and this data should be confirmed in larger population.

Furthermore, literature on graft survival and pregnancy focuses on comparisons with matched control groups of women who did not get pregnant [3]. In most studies no differences were reported, and authors conclude that graft survival is rather good after pregnancy. This is a correct statement but it is essential for counseling to mention that more than 40% of the women are back on dialysis before their child is leaving Elementary School (figure 1).
We think that it is important to mention during counseling that a substantial group of women lose their graft in a short term after delivery and based on our data almost

one out of eight mothers die before their children reach adulthood. Female KT recipients with a desire to have children should be informed that they might have to raise their children under difficult circumstances and have an increased morbidity and mortality after delivery.

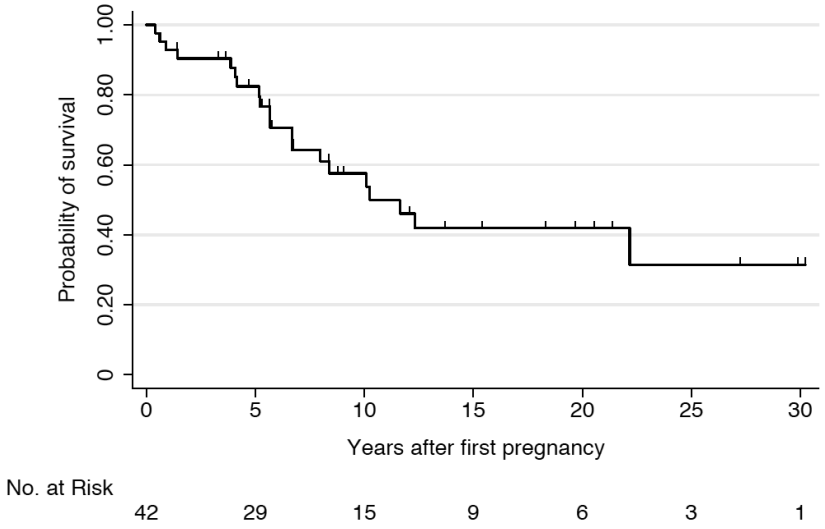

Figure 1: Estimated Kidney Graft Survival after First Pregnancy, censored for death.

References

1. Sibanda N BJ, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: A report from the UK transplant registry. *Transplantation.* 2007;83(10): 1301-1307.
2. Deshpande NA JN, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Montgomery RA, Segev DL. Pregnancy Outcomes in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis. *American Journal of Transplantation.* 2011.
3. Stoumpos S, McNeill SH, Gorrie M, et al. Obstetric and long-term kidney outcomes in renal transplant recipients: a 40-yr single-center study. *Clin Transplant.* 2016;30(6): 673-681.
4. Gaalen van R. Jaarlijks verliezen ruim 6 duizend minderjarige kinderen een of beide ouders [Internet]. CBS Nederland; 2013. Available from: https://www.cbs.nl/nl-nl/nieuws/2013/32/jaarlijks verliezen-ruim-6-duizend-minderjarige-kinderen-een-of-beide-ouders
5. Stoumpos S, McNeill SH, Gorrie M, Mark PB, Brennand JE, Geddes CC, et al. Obstetric and long term kidney outcomes in renal transplant recipients: a 40-yr single-center study. Clin Transplant. 2016;30(6):673-81.

Chapter 6

EXPloring attitudes and factors influencing reproductive Choices in kidney Transplant patients (The EXPECT-study)

Marleen C. van Buren, Denise Beck, A. Titia Lely, Jacqueline van de Wetering, Emma K Massey

Clin Transplant. 2021: e14473

ABSTRACT

Pregnancy can have risks after kidney transplantation (KT). This mixed-methods study aimed to identify the percentage of women getting pregnant after KT and explore motives for and against pregnancy together with psychosocial and medical factors involved in decision making. Furthermore, experiences of pregnancy and child-raising were explored. Women who got pregnant after KT were matched with women who had not been pregnant after KT. Semi-structured interviews were conducted, transcribed verbatim and analyzed using directed content analysis. After KT only 12% of women got pregnant. Eight women with pregnancies after KT were included (P-group) and matched with 12 women who had not been pregnant after KT (NP-group). Women after KT experienced a high threshold to discuss their pregnancy wish with their nephrologist. The nephrologists' advice played an important role in decision-making, but differed between the groups. In the P-group a desire for autonomy and positive role models were decisive factors in proceeding with their pregnancy wish. In the NP-group disease burden and risk perception were decisive factors in not proceeding with their pregnancy. Nephrologists need to be proactive in broaching this subject and aware of factors influencing the decision and outcomes. Standardized preconception guidelines on pregnancy counseling are recommended.

INTRODUCTION

Chronic kidney disease (CKD) negatively affects fertility. One of the benefits of kidney transplantation (KT) is the potential recovery of fertility. Women after KT have the same desire to become mothers as those in the general population [1,2]. Successful pregnancy after KT is possible but there is an increased risk of complications for mother and child [3,4]. Pregnancies after KT compared to the general population are associated with higher rates of preterm deliveries, growth retardation and low birth weight [3]. Maternal complications can include hypertension and increased risk of pre-eclampsia [5]. Preconceptional international guidelines recommend that women after KT should have 1. stable kidney function, 2. no active infections, 3. are not taking teratogenic medications, and 4. immunosuppressive medications (IM) are at maintenance levels [6,7]. Although evidence suggests that pregnancy does not decrease graft survival [8], mothers can be faced with dialysis or re-transplantation and their families can be faced with the loss of a parent/partner [9].

Despite the importance of the topic, there are only a few qualitative studies on perspectives on pregnancy among women who have undergone KT. One review described decision-making themes among women with CKD, however, studies included were limited by the fact that pregnancy was not the primary focus and heterogeneity of their samples [10,11]. To date, only one qualitative study has focused specifically on pregnancy among women with CKD in Australia [12]. The authors concluded that decisions about pregnancy in the context of CKD require women to think about their own survival, disease status and possible guilt towards their family. This study was informative, however, patient in all stages of CKD were grouped together and experiences of raising children after KT were not investigated.

Given the limited research on pregnancy after KT, this mixed-methods study aimed to explore (a) which percentage of women transplanted at a fertile age get pregnant after KT (b) the motives and decision-making regarding pregnancy after KT among women who got pregnant compared to women who explicitly chose not to get pregnant and (c) the experience of being pregnant and child-raising after KT.

METHODS

Study design

This was a single-center, mixed-methods study. We conducted a quantitative retrospective review of medical records to create the total cohort of women who were transplanted to describe childbearing after KT. We conducted a descriptive analysis of the characteristics of this cohort. From this total cohort we generated a subset

of patients for the qualitative analysis to explore pregnancy decision-making and childrearing experiences after KT. Guidelines for qualitative research as described in the Coreq guidelines and the Patient and Educational Counseling editorials were followed [13-16].

Ethical approval from the Institutional Review Board of the Erasmus Medical Centre was obtained (MEC-2016-144). Procedures were conducted in accordance with the Helsinki Declaration (version 2013).

Participant Selection and Setting

We created a total cohort from patients transplanted at the Erasmus Medical Center between 1974-2016 using the following inclusion criteria: female, aged 45 years or younger at time of KT (**Figure 1**).

For the qualitative subset of the cohort, women were selected using the following inclusion criteria: a pregnancy of at least 20 weeks after KT, and a functioning graft at time of screening . We excluded women who already had children before KT because this might have influenced the decision-making process. Patients who were cognitively impaired, could not speak Dutch or were diagnosed with primary infertility were also excluded.

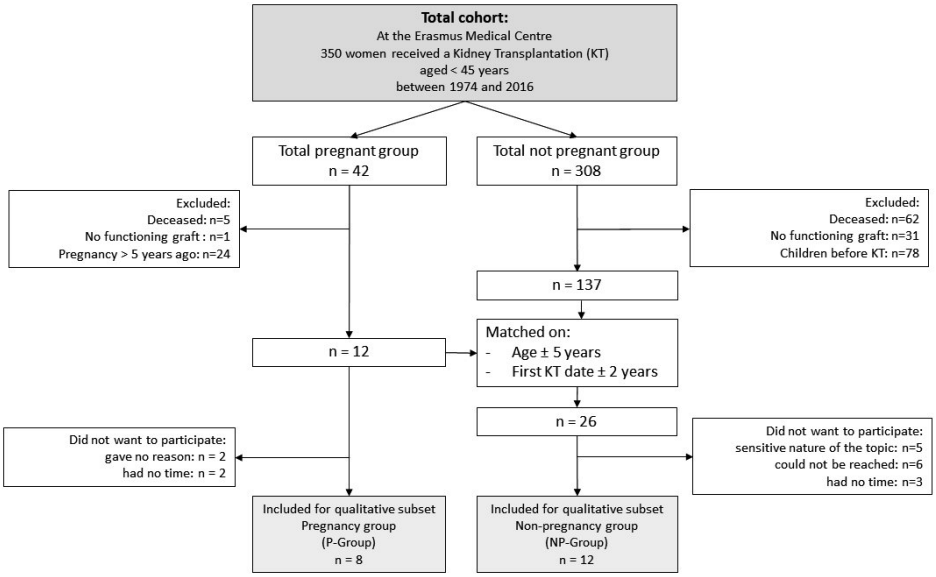

Figure 1: Flowchart

We approached women for participation in 2016. To avoid recall bias we only included women who were pregnant in the previous 5 years (Pregnancy group (P- group)). These women were matched on age (± 5 years) and time of first transplantation (± 2 years) with women who had not become pregnant (Non-Pregnancy group (NP-group)).

We anticipated that the number of women who satisfy the criteria for inclusion in the P-group would be small. The goal was to include a minimum of 6 participants to have sufficient information power [17-19] . We anticipated that there would be a larger pool who would be eligible for the NP-group, however, as this group was matched with the P-group the same goal of 6 participants was set.

Data collection

Total cohort

Medical records of women aged 45 years or younger at the time of KT were examined to assess diagnosis of CKD, year of first KT, age at first KT, presence of children before KT, death, age at death, years KT to death, years delivery to death, years since last KT, number of grafts lost, age at last KT, graft loss since last KT, years KT to graft loss, years first delivery to graft loss.

Qualitative subset

Potential participants were approached by letter. Patients could indicate their wish to participate by returning the signed informed consent form in the pre-paid envelope supplied. If no consent form was returned after two weeks, women were approached by telephone to assess willingness to participate. Women who consented to participation were contacted by telephone to make an appointment for the interview. The interviews were performed at the outpatient clinic.
The interview guide was developed based on literature and expert opinion (Appendix 1). Two researchers independent from the care team conducted semi-structured interviews between April and November 2016 (MB, DB). The women who participated in the interviews were asked to complete a questionnaire on demographic and obstetric characteristics.

Data Analysis

The total cohort was analyzed using SPSS 27.0. Firstly, we tested whether women who got pregnant after KT differed from women who did not get pregnant after KT on type of kidney disease, year of first KT, age of first KT, children before KT, death, age at death, years KT to death, years since last KT, total number of KT, age

at last KT, graft loss since last KT, years KT to graft loss using chi-square tests or Mann-Whitney tests.
The interviews conducted among the subset of the cohort were recorded, transcribed verbatim and imported into ATLAS.ti software [20]. We used direct content analysis, which is a combination of deductive and inductive analysis, according to the Coreq guidelines[10] [16,21,22]. MB and DB coded the transcripts independently. After coding the transcripts, the individual codes were compared and discussed until consensus was reached. When necessary, a third researcher was involved (EM). Descriptive statistics were used to describe the socio-demographic and pregnancy outcomes (if applicable) of the women in the subset of the cohort.

RESULTS

Total cohort

Between 1974-2016, 350 women ≤ 45 years underwent a KT at the Erasmus MC (**Figure 1**). Only 42 women (12%) gave birth after KT. In this cohort, women who got pregnant after KT were transplanted at a younger age and therefore had longer follow-up time than those who did not get pregnant (p=0.00). Mortality did not differ significantly between the groups although time between first KT and death was significantly longer in the group who got pregnant after KT (P = 0.05) (**Table 1**). Women who got pregnant after KT had undergone a greater total number of transplants than women who did not get pregnant (p=0.04).

Table 1: Characteristics of the total cohort of women transplanted < 45 years at the Erasmus Medical Centre

	Total pregnant group (n=42) n (%)	Total not pregnant group (n=308) n (%)	P value X^2/ mann-whitney test
Basic characteristics At time of screening: 01-07-2016			
CKD[1] diagnosis/cause (n)			0.16
- Diabetes 1 or 2	1 (2%)	27 (9%)	
- Systemic lupus erythematosus	2 (5%)	19 (6%)	
- Focal segmental glomerulosclerosis	3 (7%)	18 (6%)	
- other immunological disease	7 (17%)	51 (17%)	
- Urological	11 (26%)	39 (13%)	
- Other congenital	3 (7%)	11 (4%)	

Table 1: Characteristics of the total cohort of women transplanted < 45 years at the Erasmus Medical Centre *Continued*

	Total pregnant group (n=42) n (%)	Total not pregnant group (n=308) n (%)	P value X^2/ mann-whitney test
- Cystic Disease	0	22 (7%)	
- Hypertension	1 (2%)	23 (7%)	
- Other	10 (24%)*	59 (19%)**	
- Unknown	4 (10%)	39 (13%)	
Age at first KT[2] (median, IQR[3])	21 (13)	34 (16)	**0.00**
Age at last KT (median, IQR)	29 (18)	36 (15)	**0.00**
Years since first KT (median, IQR)	25 (13)	13 (12)	**0.00**
Years since last KT (median, IQR)	14 (19)	11 (11)	0.06
> 1 KT	21 (50%)	104 (34%)	**0.04**
Women who had children before KT	0	114 (37%)	**0.00**
Death	5 (12%)	62 (20%)	0.20
Age at death (median, IQR)	40 (11)	45 (17)	0.36
Years first KT to death (median, IQR)	19 (13)	9 (8)	**0.05**
Years first delivery to death (median, IQR)	6 (17)	n/a	
Graft loss[4] since last KT	1 (2%)	64 (21%)	**0.00**
Years last KT to graft loss (median, IQR)	0.04 (n/a)	2 (6)	0.43
Graft loss after first delivery	20 (48%)	n/a	
Years first delivery to graft loss (median, IQR)	6 (6)	n/a	

X^2 : chi-square, CKD: Chronic kidney disease, KT: Kidney Transplantation, IQR: inter quartile range, DCGL: Death Censored Graft Loss

*Tubular interstitial nephritis ECI (6), Rapidly progressive glomerulonephritis without systemic disease (2), Acute tubular necrosis (1), Bartter/Gitelman (1),

**Glomerulonephritis ECI (15), HUS-TTP (13), Bartter/Gitelman (5), amyloidosis (4), rapidly progressive glomerulonephritis without systemic disease (4), HELLP/preeclampsia (3), acquired obstructive nephropathy (3), Acute tubular necrosis (2), drug-induced acute interstitial nephritis (2), nephrectomy due to trauma (2), nephron-calcinosis (1), post-streptococcus glomerulonephritis (2), primary oxalosis (1), renal-vascular not specified (1), ciclosporin toxicity (1),

Qualitative subset

In total 20 women were interviewed. Enough information power was reached in both groups[19]. Women in both groups had median age of 20 years (IQR 14) at their first KT and a median age of 36 years (IQR 7) at the time of the interview. At their most recent KT women had a median age of 30 years (IQR 15).

Pregnancy group (P-group)

During the study period we identified 12 eligible patients who had been pregnant in the last 5 years, and had a functioning graft; 8 participated. The characteristics of participants and outcomes of their pregnancies are shown in **Table 2**. The majority of pregnancies were complicated by preeclampsia. There was a trend towards higher education in the P-group compared to the NP-group (p = 0.07).

Non-pregnancy group (NP-group)

We matched 26 women who had not been pregnant (NP-group) after KT based on time of transplantation and age. Twelve of these women agreed to participate. **Table 2** shows that study participants of the NP-group had a higher number of co-morbidities (p = 0.03), and were less likely to be in paid employment at the time of the interview than the P-group (p=0.04).

Themes

Post-transplant pregnancy decision-making

We identified 10 themes on pregnancy decision-making: desire for children, timing, risks, role of the nephrologist, role of the social network, autonomy, disease burden, alternatives for pregnancy, religion, and positive role models. Illustrative quotations are provided in **Table 3** per theme.

Table 2: Demographic characteristics and pregnancy outcomes of qualitative subset

Women	Pregnancy group 'P Group' (n=8)	Non pregnancy group 'NP group' (n=12)	P value X^2
Age at time of interview (median, IQR)	36 (12)	36 (4)	0.91
Age at first KT (median, IQR)	21 (13)	19 (14)	0.10
Age at last KT (median, IQR)	30 (12)	26 (16)	0.47
Living with partner[1]	8 (100%)	10 (83%)	0.22
Higher education[2]	7 (100%)*	7 (64%)	0.07
Paid job	6 (86%)*	4 (36%)	**0.04**
Declared unfit for work	0*	4 (36%)	0.07
Adoption/foster child	0	4 (33%)	0.07
CKD[4] diagnosis or cause			
-immunological disease	3 (37%)	7 (58%)	0.84
-urological/congenital	3 (37%)	4 (33%)	
-other	2 (25%)*	1 (17%)**	

Comorbidities	2 (25%)	9 (75%)	**0.03**
Pre-emptive KT	2 (25%)	7 (58%)	0.14
Living donor KT	7 (88%)	11 (92%)	0.76
>1 KT	3 (38%)	8 (67%)	0.20

Pregnancy Outcomes	
Total pregnancies	13
- Live birth	12 (92%)
- IUFD at 20 weeks	1 (8%)
Assisted Pregnancy[3]	3 (23%)
Hypertensive disease in pregnancy	10 (77%)
- Gestational hypertension	2 (15%)
- Preeclampsia	8 (62%)
Gestational age, weeks (median, IQR)	37 (2)
Birth weight, grams (median, IQR)	2775 (848)
Hospitalization during pregnancy [4]	11 (85%)
Mode of delivery	
- Spontaneous vaginal delivery	7 (54%)
- Vacuum assisted vaginal delivery	2 (15%)
- Cesarean delivery	4 (31%)

*Focal segmental glomerulosclerosis, nephronophthisis, **hodgekin lymfoma

X^2: chi-square, IQR: Inter Quartile Range, KT: Kidney transplantation, CKD: Chronic Kidney Disease, IUFD: Intra Uterine Fetal Death,

[1]at time of the interview, [2]Senior general secondary education/secondary vocational education, [3]IVF(In Vitro Fertilization)/ICSI (Intracytoplasmic Sperm Injection)/hormone treatments, [4]Antepartum,

Table 3. Considerations prior pregnancy after Kidney Transplantation

Themes	Quotations Pregnancy (P) group	Non-pregnancy (NP) group
Desire for children		
Reason of child wish?	"so that if you're grown up or may grow old, that there are people who can take care of you" "that was how I saw myself, with children" "to make our family or happiness complete" "to seal the love between us"	"if I was healthy, I would have wanted kids" "it is lonely not having kids; it is hard when you stay together without kids"
Timing/ preparation		
Timing	"it is best to become pregnant within 5 years after your kidney transplantation"	"I still want to get pregnant but now I am 43 and I am not going to start with it anymore."
Risks		
Heredity	"we did not want to get a child who has the same disease" "inherited disease not a reason not to have children"	"the risk of giving an inherited disease to a child is 50%, so that is quite something..."
Medication switch	"medication switch not a problem" "first we both got tested if we were fertile, then we switched the medication"	"kidney was rejected because of the medication switch" "the risk for the kidney..., when you change your medication for pregnancy, it's not worth the risk"
Risk for the child	"it can be born small and too early; I don't mind this if the child is healthy" "medication is the only risk for the child" "medication not a problem, without medication it is not possible at all"	"I use tacrolimus and mycophenolate acid and I read on the internet that the child would not have ears or fingers... That's when I thought, forget it..."
Risk for the graft	"to have a child is worth the decline in kidney function"	"I just want to keep my kidney! I absolutely don't want to lose it" "I think it would take more effort for the kidney to support two body's and I think it will get crushed..." ".. the chance that my kidney function stays good forever isn't already that big... and I have already lost a kidney..."
Trust in good outcome	"I just took a leap of faith"	

Table 3. Considerations prior pregnancy after Kidney Transplantation *Continued*

Themes	Quotations Pregnancy (P) group	Non-pregnancy (NP) group
Nephrologist		
Influence of nephrologist	"it is possible but they don't recommend it… That was a real downer… that bothered me for quite a long time…" "'I did not want to let him/her down" "very discouraging" ''the nephrologist did not bring the subject up him/herself" "the nephrologist was very positive, I wonder if they knew the real impact" " I got pregnant against his/her advice"	".. if you do get pregnant you should take into account that you are not able to see it grow old. That sentence had a huge impact on me" "the decision not to have children was decision of my own, but nephrologist agreed with me"
Social network partner/donor/peers		
Involvement of others	"I took the decision with my parents" "only my husband was involved"	"together we decided not to have a child"
Influence of living donors	"my brother (donor) thought… what are you doing…" "my mother (donor) asked me why do you want another child, you are very lucky that you have one!"	
Peer contacts	"I shared my experiences with my transplant friend"	"someone I know who is a kidney patient did not see her child reach one year old"
Reactions from the social environment	"people react very harshly, while it's none of their business, who are you to decide?" "you have already taken the risk why do it again?" "enthusiastic reactions on pregnancy"	"A good friend said, but you would be great parents!"
Parents (in law)	"it is important for our parents that they become grandparents" "my mother found it very scary"	"hard that I can't give my parents grandchildren"

Table 3. Considerations prior pregnancy after Kidney Transplantation *Continued*

Themes	Quotations Pregnancy (P) group	Non-pregnancy (NP) group
Partner	"on the same page as my partner" "he wasn't ready yet, he thought it would take years to get pregnant "he also wanted children but not on my expense"	"it's possible that your relationship gets compromised when all your energy goes to the child instead of to my partner" "my partner would have been afraid of staying alone with the child"
Autonomy/wish for normality		
Autonomy	"it's hard when someone else decides whether or not you can have a child.." ".. what I want is just going to happen!"	"it was my own decision not to get pregnant" "the disease is mine; others should not interfere with it"
Wish for normality	"because you have a kidney disease, you can't get pregnant... I thought what you can do; I can do too"	"...I don't want to be dependent on my transplant, it is quite hard for me..."
Disease burden		
Impact on daily life	"the KT has a positive impact on my life"	"at half past seven I am already asleep on the couch, raising kids would be too exhausting"
Alternatives to pregnancy		
Adoption/Surrogate	'"if you are transplanted you can't adopt, because the countries of origin think that you are going to die soon" "surrogacy goes against my religion"	"adopted children have more problems, that makes raising a child only harder" "they said to me that surrogacy is only possible if you have cervical cancer" "Since we have our foster child, I feel so good"
Religion		
	"you can lose your renal function but you don't get a child from above just like that" "then we left it to God, we gave it 6 months.	"God has the last word"

Table 3. Considerations prior pregnancy after Kidney Transplantation *Continued*

Themes	Quotations Pregnancy (P) group	Non-pregnancy (NP) group
Positive role models		
	"pregnancy of other kidney patients was a motive to go further with pregnancy" "on TV I saw a lady who already had 2 children after kidney transplantation so that's when I thought it is possible"	"...when I read on the forum that other kidney transplant patients did get successfully pregnant, it made me doubt my decision not to become pregnant.."

Desire for Children

Women in both groups wanted to have children since they were young. This desire grew with age and increasing number of peers establishing their own families. This desire encompassed caring for a child as well as being looked after in their own old age. Women also described wanting to do the things normal ('healthy') women do.

Time pressure

Time pressure was a theme reported by both groups. In the NP-group women had the feeling they had limited time to get pregnant. Additionally, these women described that by the time they felt emotionally ready for pregnancy their kidney had failed. Some concluded that they were already too old (>40 yrs) to start trying to conceive. In the P-group women described the lengthy duration of the preparation phase, for example, adjusting IM. Furthermore, attempting to get pregnant takes time. Some women received contradictory information about the length of time required to wait before getting pregnant after KT, differing from one year to a few years. One woman said that if she had known the risks associated with pregnancy after KT beforehand she would have wanted to have a child before KT.

Perception of and coping with risks

Perception of risk differed between the two groups. In the P-group, women described that they were aware of the risks, however, the wish to become a mother weighed heavier than the risks. The possibility that children might be born small and/or early was seen as acceptable as long as the child is healthy. Nevertheless, anxiety about the risks to the baby were reported. A greater number of negative considerations were reported among the NP-group compared to the P-group, including the future impact on the kidney. The NP-group described that life after KT is hard enough without children and that they did not have the energy to raise children. They also took the effect of a sick mother on a child into consideration as well as the risks of changing IM before pregnancy. One woman in the NP-group switched her IM in order to prepare for pregnancy but experienced rejection of the graft and decided not to proceed with pregnancy for fear rejecting her second kidney. Some women and their partners underwent fertility testing, to avoid unnecessarily switching of IM in case of infertility. In the P-group some women underwent genetic testing but did not have a hereditary disease.

Role of the Nephrologist

Nephrologists were reported to play an influential role in decision-making among both groups. All women described that they had to take the initiative to talk about

the possibility of having children. This was often perceived as a difficult discussion to initiate. The P-group reported receiving more positive advice and collaboration from their nephrologists than the NP-group. One woman in the NP-group discussed her wish for pregnancy but felt defeated by all the negative information and did not dare to bring up the subject again, for fear of disappointing her nephrologist.

Role of the Social network

In both groups partners played the most prominent role in decision-making. Partners were often concerned about the health of their partner and did not want a child at expense of the mother. For some women in the NP-group, guilt towards their partner was the decisive factor. Parents played a less important role in the decision, but were in most cases supportive of pregnancy. Living donors were reported to have expressed their concerns about the risks to the kidney during pregnancy. In both groups women reported feeling a sense of responsibility towards their living donor and reluctance to take unnecessary risks. Women also described they would like to come in contact with other recipients to discuss this subject.

Autonomy

Autonomy was a commonly reported theme in the P-group. They expressed the need to be autonomous and take responsibility to avoid the feeling that someone else (health care professionals) has control over decisions regarding their body. In the NP-group women described how difficult it is when someone else decides whether or not you can have children. In the P-group women felt that despite the KT they still had an element of choice. The NP-group felt dependent on their transplant and thus less autonomy to decide.

Disease burden

The P-group described that CKD had (initially) little impact on their daily lives. However, CKD started to play a bigger role when they developed a wish for children. While in the NP-group CKD already had a big influence on their daily lives; complaints included fatigue, side-effects of the medication and stress about the functioning of the transplant. Also, they described having undergone multiple KT's from multiple living donors and not wanting to put their kidney at risk. This is in line with the differences illustrated in **Table 2**.

Alternatives for pregnancy

In both groups women had explored other options to pregnancy during the decision-making process such as adoption and IVF. These options were seen as less pref-

erable. In the NP-group, 4 women had a foster child and 1 was planning on adopting a child at the time of the interview. None of the participants chose surrogacy, partly because the Dutch law and regulations are very strict. Adoption was not always possible, because of their CKD. Of the women who did not opt for an alternative, reasons were fatigue, not wanting a child to have a sick mother, and partners being against it.

Religion

Some women in both groups reported having a religious affiliation but that religion did not play a role in their desire for children and pregnancy. Religion did play a role in the decision not to go forward with surrogacy as that would be against their religion. Additionally, women with a religious affiliation reported the belief that having a child is in the hands of God.

Positive Role Models

Women in the P-group described that when they saw stories in the media about pregnancy after KT they realized that it was possible. Stories of other transplant recipients who had gone through pregnancy were a source of information and support. These role models triggered them to proceed with their wish for pregnancy. In the NP-group these stories made them doubt their decision not to get pregnant.

Experiences of pregnancy, delivery and raising children after Kidney Transplantation

In the second part of the study we focused on the experiences of pregnancy, delivery and child-rearing among women in the P-group. In general, women were happy with their decision to have children, although some felt that they had underestimated the impact and at times even regretted their decision. These themes are described in the following section and illustrative quotations are provided in **Table 4**.

Experience of complications during pregnancy

Most of the women had a good start to their pregnancy, complications begun when they were ≥ 20 weeks pregnant. In the majority of the pregnancies in this cohort, preeclampsia was diagnosed. Women who were asymptomatic found it difficult to understand or accept the treatment recommendations or the need to be admitted to the hospital. Women reported that communication between gynaecology and nephrology department was not always transparent for them.

Fear of damage to kidney transplant

Women described being afraid of potential damage to their kidney during contractions and labor. One woman worried about pain at the location of her transplanted kidney at the end of her pregnancy because her child was pushing on it.

Deterioration graft function after delivery

Impairment in graft functioning was something multiple women experienced after their delivery. This differed from mild to severe deterioration for which dialysis was required. Some had emergency deliveries due to fetal distress and reported the feeling that their graft was damaged during the delivery. Dialysis was very hard for one young mother as she described not feeling part of her family anymore. Also, some women had to be re-transplanted soon after their delivery. This was something they had not taken into account when they considered pregnancy.

Child raising burden

Experiences of raising children varied from feeling very capable to the feeling that they were struggling; ranging from a great experience to not being able to handle it physically and mentally. Mothers who suffered from fatigue, in particular, described raising children as very hard. Women also worried about what the impact of having a sick mother might be on a young child. Another fear was not getting to see their child grow up.

Second child after KT

Half of the woman in the P-group had had a second child after KT. With their second child mothers were more concerned about the risks because they understood the responsibilities of being a mother. Women who did not proceed with trying to have a second child stated that they did not want to deliberately put their health at stake, fearing they cannot be a good mother anymore. Women who had two children described high levels of child raising burden.

Impact on employment

Mothers described that, after they had children, working was too much because they lacked the energy. The majority sought alternative employment that required less effort and some stopped working altogether.

Social Network

Having a supportive social network was described as very important by all mothers. Women relied on their network when they were too tired to look after their child(ren)

or when they were hospitalized. Women highlighted the necessity of a helpful partner that can take over when they are low on energy.

Table 4. Experiences of pregnancy, delivery and raising children after Kidney Transplantation

Themes	Quotations
Pregnancy	
	"pregnancy was only complicated at the end" "it went well but suddenly there was preeclampsia" "only at the end of my pregnancy it affected my kidney because the child was pushing on it" "...you need to hang in there, at 26 weeks it is possible, then they performed an ultrasound and there was nothing anymore..." "despite the complications I did not feel bad during my pregnancy"
Delivery	
	"I was afraid to push because of my kidney therefore I finally got a caesarian section" "I lost 3 liters of blood" "the delivery should happen very quickly because the baby had shortness of oxygen and hadn't descended, it all ended well, but my kidney has been majorly damaged by it all"
Deterioration graft function after delivery	
	"when I was on dialysis it was like I was not part of family life anymore..." "I thought my baby would be older when I would need another kidney" "then my kidney got rejected, and there I was in the hospital with my little baby"
Raising children	
	"they ask me if I could handle it all in my situation, but I did not want to hear that..." "I was afraid that I would not see my child grow up" "now I understand why people choose deliberately not to get pregnant" "tiredness is a handicap" "when it all goes well it is fine, but it just doesn't always go well" "I am not looking forward to the moment when they get teething problems..." "it is often at my expense; I have largely disappeared. I really just survive now" "I am afraid of what the effect of a sick mother has on my children"
Second child	
	"one child is enough for me" "raising my first child went fine, with a second child it is very tough" "I would have wanted to know beforehand, what the impact was of a second child" "with my first pregnancy I was not afraid to lose my kidney, but now with my second pregnancy I am worried, because I am a mother now"
Children, transplantation and work	
	"working and also have kids was too much" "when you have cancer there are guidelines how much you can work, on working after KT there are no guidelines, this uncertainty was a real problem for me"
Importance of social network	
	"it is hard, because my partner is my new donor..." "after dinner, my partner takes over" "it is very important to have a social safety net"

DISCUSSION

This is the first study to explore the thoughts of both women who decided to try to get pregnant after KT and those who decided not to. This mixed-method study demonstrated that only 12% of the women transplanted at a fertile age got pregnant after KT. Furthermore, women who became pregnant after KT were generally more healthy than those who did not. One of the most striking finding is that, even now at a time when patients are more empowered than ever before, patients in our study still experienced reluctance to discuss their pregnancy wish with their nephrologist. Nephrologists played a crucial role in both groups but differed in their attitude towards pregnancy after KT. Women reported feeling defeated by all the negative information. This emotionally overwhelming situation was also described by Wiles [23]. In this study the type of advice and the decision to try to get pregnant depended very much on the knowledge and attitude of the nephrologist towards pregnancy. Advice on timing of the pregnancy varied.

Arguments for pregnancy were positive role models, desire for normality and autonomy. It is a known effect that individuals who are more autonomous and want to pursue desirable outcomes are most inspired by positive role models [24]. Women were striving for normality and felt that being able to bear children made them feel closer to normality. This phenomenon was also described in a study in which women described their chronic illnesses as deviations from normality and their pregnancies brought them closer to normality [25].

In our study women reported disease burden, comorbidities and perception of/and coping with risks as decisive reasons for not trying to get pregnant after KT. Perception of risks also appeared to differ between the two groups. As the NP-group experience a higher disease burden than the P-group, they were more focused on minimizing risks and preventing poor outcomes. Women in the NP-group seemed to look beyond the pregnancy itself, they thought more about their ability to raise a child, as well as the impact on the graft, child and partner. Of interest was that the arguments the NP-group used against pregnancy were the same arguments the P-group used when they were considering having a second child after KT. After their first pregnancy women seemed to be more aware of the risks.

Women who got pregnant after KT reported experiencing the same difficulties as most families with young children experience. However, compared to mothers without a chronic condition they must also deal with additional considerations and limitations, such as treatment and fear of health loss. Yoshikawa and colleagues have concluded that these additional considerations and limitations do not seem to affect the quality of life in this group [26]. Among transplant recipients quality of

life is lower than the general population. Whether having children contributes to a higher or lower QoL after KT requires further investigation [27,28].

Strengths and limitations

This is the first study to address pregnancy decision-making from the perspectives of women who chose to have children and those who did not, as well as their experiences of childrearing after KT. A possible shortcoming of this unique study was that the groups were not completely comparable with regards to socio-economic status. Women who got pregnant after KT had a higher education and the majority had a paid job. Matching to control for this variable was not possible due to the low incidence of pregnancy after KT. Furthermore, financial arguments for or against pregnancy were not mentioned by the women in the interviews. Additionally, women in the NP-group had more comorbidities and a lower rate of pre-emptive transplantation than women in the P-group. While our sample with a high rate of living donors was representative of our population, we acknowledge that this may not be representative of all populations in other settings. Pregnancy after a longer period of dialysis may raise new themes. Another limitation is the small number of women included in the P-group however this reflects the small number in the cohort. Moreover, there was sufficient information power in this cohort.

CONCLUSION

Even now, despite increasing patient empowerment, women still experience reluctance to discuss their pregnancy wish with their nephrologist. The nephrologist's attitude towards pregnancy played an important role in the decision-making process but differed between women who got pregnant after KT and women who did not. In the P-group a greater desire for autonomy, normalcy and positive role models were decisive factors in proceeding with their pregnancy. Social support was an important condition for pregnancy. In the NP-group disease burden and perception of risks were decisive factors for not proceeding with their pregnancy wish. Our mixed-methods study demonstrated that pregnancy after KT is related to both objective measures of health and subjective perceptions of health.

New themes not previously described in the literature emerged from the analysis of experiences of pregnancy and raising children after KT such as dialysis or hospital admissions with young children, and trying to be a good mother when you have a chronic condition. Concessions had to be made in other areas such as career in order to be able to fulfil the chosen role as a mother alongside maintaining health and graft functioning.

Practical implications

This study shows that it is not always clear to patients what the possibilities are regarding pregnancy after KT and that advice received may depend on the knowledge and attitude of the professional. Therefore, we have four suggestions for clinical practice based on our findings:

Firstly, it is important to lower the threshold to discuss pregnancy after KT. Professionals must be aware of this problem and be proactive as women may not initiate this conversation themselves. Counseling must encompass the pros and cons and support well-informed decision-making [29]. Additionally, the period after pregnancy should be discussed. For such counseling, professionals require up to date knowledge on the subject. Further research is needed on attitudes of nephrologist and obstetricians towards pregnancy after KT. Each (transplant) center should have clear recommendations and the transplant societies need to update preconception guidelines so that clinicians have a clear and consistent message regarding parenthood after transplantation.

Secondly, to promote equal access, there is a need for accurate and standardized educational materials on becoming pregnant and having a child after KT and the implications thereof. This study shows some women seemed to think that pregnancy outcomes are generally worse than the literature supports, at least for women with adequate graft function and stable IM regimen . The gravity and consequences of this decision make it even more imperative that the advice women receive is not dependent on personal attitudes and is tailored to the patient's specific circumstances.

Thirdly, peer support programs may be beneficial for women considering pregnancy after KT. Peer support programs have been implemented amongst chronic illness patients with good results [30-32]. The extent to which peer support programs are useful and effective in this population on this topic requires further investigation.

Lastly, this study gives a voice to women who choose not to have a family after KT. Women made their decision not to get pregnant but some were clearly doubting and in need of psychological support. Counseling should also be available to these women who may have difficulty accepting their decision.

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References

1. Szpotanska-Sikorska M, Mazanowska N, Madej A, Kociszewska-Najman B, Wielgos M, Pietrzak B. Reproductive life planning in women after kidney or liver transplantation. *Clin Transplant.* 2018;32(9): e13378.
2. Crowley-Matoka M. Desperately seeking "normal": the promise and perils of living with kidney transplantation. *Soc Sci Med.* 2005;61(4): 821-831.
3. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant.* 2011;11(11): 2388-2404.
4. Moritz MJ CS, Coscia LA, et al. Transplant Pregnancy Registry International (TPR). *2017 annual report.* Philadelphia PA: Gift of Life Institute; 2018:0-21.
5. Chittka D, Hutchinson JA. Pregnancy After Renal Transplantation. *Transplantation.* 2017;101(4): 675-678.
6. McKay DB, Josephson MA. Reproduction and Transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. *American Journal of Transplantation.* 2005;5(7): 1592-1599.
7. Transplantation EEGoR. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant.* 2002;17 Suppl 4: 50-55.
8. van Buren MC, Schellekens A, Groenhof TKJ, et al. Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis. *Transplantation.* 2020;104(8): 1675-1685.
9. van Buren M, Lely T, van de Wetering J. Essential Issues for Pregnancy Counseling in Renal Transplant Women. *Transplantation.* 2018;102(6): e254.
10. Tong A, Jesudason S, Craig JC, Winkelmayer WC. Perspectives on pregnancy in women with chronic kidney disease: systematic review of qualitative studies. *Nephrol Dial Transplant.* 2015;30(4): 652-661.
11. Jesudason S, Tong A. The patient experience of kidney disease and pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2018.
12. Tong A, Brown MA, Winkelmayer WC, Craig JC, Jesudason S. Perspectives on Pregnancy in Women With CKD: A Semistructured Interview Study. *Am J Kidney Dis.* 2015;66(6): 951-961.
13. Finset A. Qualitative methods in communication and patient education research. *Patient Educ Couns.* 2008;73(1): 1-2.
14. Salmon P. Assessing the quality of qualitative research. *Patient Educ Couns.* 2013;90(1): 1-3.
15. Salmon P, Young B. Qualitative methods can test and challenge what we think we know about clinical communication - if they are not too constrained by methodological 'brands'. *Patient Educ Couns.* 2018;101(9): 1515-1517.
16. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* 2007;19(6): 349-357.
17. Morse JM. Designing funded qualtitative research. *Handbook of qualitative research*. 2nd ed. Thousand Oaks: Sage; 1994.
18. Creswell JW. *Qualitative inquiry and research design: Choosing among five approaches.* Second ed. Thousend Oaks: Sage; 2007.

19. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res.* 2016;26(13): 1753-1760.
20. Atlas Ti Vol Scientific Software Development GmbH. Berlin: www.atlasti.com; 2016.
21. Braun V CV. Using thematic analysis in psychology. *Qualitative Research in Psychology.* 2006;3(2): 77-101.
22. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res.* 2005;15(9): 1277-1288.
23. Wiles KS, Bramham K, Vais A, et al. Pre-pregnancy counseling for women with chronic kidney disease: a retrospective analysis of nine years' experience. *BMC Nephrol.* 2015;16: 28.
24. Lockwood P, Jordan CH, Kunda Z. Motivation by positive or negative role models: regulatory focus determines who will best inspire us. *J Pers Soc Psychol.* 2002;83(4): 854-864.
25. Tyer-Viola LA, Lopez RP. Pregnancy with chronic illness. *J Obstet Gynecol Neonatal Nurs.* 2014;43(1): 25-37.
26. Yoshikawa Y, Uchida J, Akazawa C, Suganuma N. Associations between physical and psychosocial factors and health-related quality of life in women who gave birth after a kidney transplant. *Int J Womens Health.* 2018;10: 299-307.
27. Wei TY, Chiang YJ, Hsieh CY, Weng LC, Lin SC, Lin MH. Health related quality of life of long-term kidney transplantation recipients. *Biomed J.* 2013;36(5): 243-251.
28. Dobbels F, De Bleser L, De Geest S, Fine RN. Quality of life after kidney transplantation: the bright side of life? *Adv Chronic Kidney Dis.* 2007;14(4): 370-378.
29. Snoek R, van der Graaf R, Meinderts JR, et al. Pregnancy in Advanced Kidney Disease: Clinical Practice Considerations on a Challenging Combination. *Nephron.* 2020;144(4): 185-189.
30. Dennis CL. Peer support within a health care context: a concept analysis. *Int J Nurs Stud.* 2003;40(3): 321-332.
31. Harris GE, Larsen D. HIV peer counseling and the development of hope: perspectives from peer counselors and peer counseling recipients. *AIDS Patient Care STDS.* 2007;21(11): 843-860.
32. Embuldeniya G, Veinot P, Bell E, et al. The experience and impact of chronic disease peer support interventions: a qualitative synthesis. *Patient Educ Couns.* 2013;92(1): 3-12.

Appendix 1: Semi-structured interview guide (EXPeCT study)

Instructions

You have been invited for an interview because we are interested in reasons why women become pregnant or not after kidney transplantation.
The topics we will discuss include factors that influenced this decision.
What you tell me is confidential and will be reported anonymously. This means that your name will not be mentioned.
To be able to process this interview, I will record our conversation.
There are no right or wrong answers, it is about your experience and your opinions that are very valuable for us. We hope in the future we can improve the care we offer to our patients.
Do you have any questions before I begin?

Opening questions (15 minutes)

1. What kind of impact does your kidney disease and kidney transplantation have on your life?
2. Do you have a partner now? Did you have a partner at the time of the kidney transplantation?
3. From the questionnaire it seems that you have (not) been pregnant in the past.

a. Was this a conscious choice? (planned/hoped-for)?

4. Do you have a desire to get pregnant now?
5. Can you tell me something about your motives to become pregnant or not after kidney transplantation?

Medical factors (15 minutes)

Firstly, I want to ask you about the medical considerations.

1. Does the kidney transplantation have an effect on your decision to become pregnant or not? Can you tell me why?
2. Were there medical factors involved in your considerations to become pregnant of not? Which ones?
3. Do you have the feeling that you have enough knowledge about the possible risks of pregnancy after kidney transplantation?

a. Can you describe possible risks that could occur for yourself and your kidney transplant?

4. And what kind of risks there are for the baby?
5. Which of these risks were the most important for your decision? Can you tell me why?
6. Did the immunosuppressive drugs you have to take play a role in your decision?
7. Are their known genetically transmitted diseases in your family?

a. If this is the case, have you been sent to the department of clinical genetics?
b. Was this your own initiative?
c. How did this go?

Social factors (15 minutes)

1. Besides the medical factors did you experience other feelings, fears or worries that were influential for your decision to become pregnant or not?

a. Wish for a child / Your partners wish for a child? Did you feel the same about this?
b. Was your age or your partners age influential in your decision-making?
c. Was religion or meaningfulness important in your decision-making process?

2. Which people in your social network influenced on your decision to become pregnant or not?

a. What was the role of your partner?
b. What was the role of your nephrologist?
c. What was the role of your nurse/ nurse practitioner?
d. What was the role of other medical specialists/ general practitioner?
e. What was the role of family members/ friends?
f. What was the role of the donor (if applicable)
g. What was the role of other patients? (social media, patient society)

Guidance from a professional (15 minutes)

The next questions will discuss the way you experience guidance from a professional for your wish for a child at the Erasmus Medical Center.

1. Was your possible desire for children discussed before your kidney transplantation?

a. Who took the initiative? (you, nephrologist, nurse/nurse practitioner, other)
b. What was the advice?
c. How did you deal with this?
d. Were you content with this or did you feel it could have been better?

2. Was your possible desire for children discussed after your kidney transplantation?
a. Who took the initiative? (you, nephrologist, nurse/nurse practitioner, other)
b. What was the advice?
c. How did you deal with this?
d. Were you content with this or did you feel it could have been better?

3. Did you have an appointment at the pre-conceptional outpatient clinic of the gynecology department?
a. Was this influential on your decision to become pregnant or not?
4. Did you discuss alternatives for pregnancy such as adoption or surrogacy?
a. With whom did you discussed this?
b. What were your considerations for choosing this or not?

The next questions are only applicable for women who were pregnant after kidney transplantation:

1. What was the most important consideration for trying to get pregnant and why?

2. How did your network react on your decision of trying to get pregnant?
a. To what extent did your kidney transplantation affect the reactions of those in your network? Was this an issue?

The course of your pregnancy/ pregnancies

1. Did you discuss your desire to get pregnant before conception?
a. At what moment was this?
b. When you were considering or when you were already trying to get pregnant?

2. Was your medication regime altered before you got pregnant? Or was this already during your pregnancy?
a. Did you take other measures?

3. How did you feel about taking immunosuppressive drugs while you were pregnant?
a. What were your considerations?
b. Did this effect the way you experienced your pregnancy?

4. You have been transplanted and become pregnant; How do you feel about this? (subquestion) How did you experience your pregnancy / pregnancies.

5. What influence did your kidney transplantation have on your pregnancy?
6. Do you think that the pregnancy affected your kidney function/ transplant survival?
7. What are your plans for future pregnancies? (subquestion) What were your considerations?
8. How did your partner experienced the pregnancy do you think?

Raising children

1. What are your experiences on raising children after kidney transplantation?

a. Are there advantages?

b. Are there disadvantages?

Other questions & closing

1. Do you have anything to add? (Are there things that are not discussed on this subject that you want to talk about?)
2. Any other questions or remarks on this conversation?

When this study is finished you will receive a summary of the most important findings. When you have any questions in response to this interview, you can turn to the researcher Marleen van Buren

Thank you for your participation!

PART 4

Summary, Discussion and Appendices

Chapter 9

Summary

Summary and conclusions

The overall aim of this thesis was to give an overview of pregnancy outcomes after kidney transplantation. In addition, we provided an insight in pre-conceptional? counseling procedures, experiences of both patients and professionals and finally the pregnancy outcomes after living kidney donation. The PARTOUT (Pregnancy After Renal Transplant OUTcomes) network was established for the purpose of data collection from all pregnancies after kidney transplantation (KT) in the Netherlands

PART I

In **Chapter 2** we performed a meta-analysis and systematic review on graft loss (GL) and graft function, measured by serum creatinine (SCr), after pregnancy in KT recipients. Our search yielded 38 studies on GL of which 10 studies compared outcomes with nulliparous KT recipients and 18 studies on SCr. The pooled incidence of GL was respectively 9.4% within 2 years after pregnancy, 9.2% within 2–5 years, 22.3% within 5–10 years and 38.5% >10 years. In addition, our data showed that, in case of graft survival, SCr remained stable over the years. Only within 2 years postpartum, Δ SCr was marginally higher (0.18 mg/dL, 95% Confidence Interval (CI) [0.05-0.32], P = 0.01). Furthermore, no differences in GL were observed in studies comparing GL after pregnancy with nulliparous controls. Systematic review of the literature showed that mainly pre-pregnancy proteinuria, hypertension, and high SCr are risk factors for GL. Therefore we concluded that pregnancy after KT has no effect on long-term graft survival and no significant differences were observed between pre- and postpartum SCr at longer follow-up intervals. A possible effect on graft function was only observed within 2 years postpartum, which might be due to publication bias.

Subsequently we established the national PARTOUT dataset to analyze the effect of pregnancy on graft function and pregnancy outcomes. The results of these two multicenter cohort studies are described in **Chapter 3 and Chapter 4.** In **Chapter 3** we described multilevel analyses to study the effect of pregnancy on eGFR after KT. Changes in eGFR before and after each pregnancy were analyzed by generalized estimating equations (GEE) multilevel analysis adjusted for transplant vintage. Women were their own control group. We included 3194 eGFR measurements before and after pregnancy in 109 (55%) KT-recipients with 1, 78 (40%) with 2, and 10 (5%) with 3 pregnancies after KT. Median follow-up after first delivery post-KT was 14 y (interquartile range, 18 y). Adjusted mean eGFR pre-pregnancy was 59 mL/min/1.73 m2 (SEM [Standard Error of the Mean] 1.72; 95% confidence interval [CI], 56–63), after the first pregnancy 56 mL/min/1.73 m2 (SEM 1.70; 95% CI, 53–60), after the second pregnancy 56 mL/min/1.73 m2 (SEM 2.19; 95% CI, 51–60), and after

the third pregnancy 55 mL/min/1.73 m2 (SEM 8.63; 95% CI, 38–72). Overall eGFR slope after the first, second, and third pregnancies was not significantly worse than pre-pregnancy (P = 0.28). However, adjusted mean eGFR after the first pregnancy was 2.8 mL/min/1.73 m2 (P = 0.08) lower than pre-pregnancy. Furthermore we tested if eGFR decreases faster after pregnancy by inluding the interaction term 'Transplant vintage (years)*after pregnancy' to the model. This was also not significant worse after first pregnancy (p= 0.29) after second pregnancy (p=0.08) and after third pregnancy (p =0.39). We concluded that first pregnancy after KT has a small, but insignificant, effect on eGFR slope in after KT. Midterm hyperfiltration, a marker for renal reserve capacity, was associated with better eGFR and death-censored graft survival. In this KT cohort with long-term follow-up, no significant effect of pregnancy on kidney function was detected.

In **Chapter 4** we described the outcomes of pregnancy after KT in the Netherlands. This multicenter cohort study was also performed with data from the PARTOUT network. Outcomes were analyzed per pre-pregnancy eGFR-category. To identify risk factors for adverse pregnancy outcomes a composite adverse pregnancy outcome (cAPO) was established: birthweight <2500 gram, preterm birth <37 weeks, 3rd trimester severe hypertension (SBP >160 and/or DBP >110 mmHg) and/or >15% increase in serum creatinine (SCr) during pregnancy. 288 singleton pregnancies in 192 women were included. Total live birth was 93%, mean gestational age 35.6 weeks, mean birthweight 2383 gram. Independent risk factors for cAPO were pre-pregnancy SCr, midterm percentage SCr drop and midterm mean arterial pressure (MAP) drop ; ORs 1.01 (95% CI 1.00-1.02), 0.95 (0.91-0.98) and 0.94 (0.90 to 0.98). cAPO was a significant risk indicator for graft loss (HR 2.55, 1.09 to 5.96). This study resulted in clinically relevant and novel data on pregnancy outcomes after KT per pre-pregnancy eGFR-category ideally suited for counseling young KT-recipients. The overall obstetric outcomes in KT-recipients are good. The Increase in maternal and neonatal adverse outcomes is mainly dependent on graft function and hemodynamic adaptation to pregnancy.

PART II

Essential issues for pre-pregnancy counseling were described in **Chapter 5, Chapter 6** and **Chapter 7.** In **Chapter 5** and **Chapter 6** single center data from the Erasmus MC were studied. In **Chapter 5** we analyzed graft survival and patient survival after pregnancy at the Erasmus MC. Median follow-up time after first delivery was 12.5 years (range, 1-34 years). During follow-up 5 (12%) of the women died 1 to 20 years after delivery (median 6 year). Ten years graft survival was 40%. Although

patient and graft survival (GS) after KT in this subgroup was longer than in our general KT population, almost one out of eight of these women (12%) did not see their child reach adulthood. In the general Dutch population, only 3.9% of the children lose one of their parents before they reach adulthood. Although graft survival was better in this subgroup, more than two out of five of these mothers (40%) are back on dialysis or in need for a re-transplant before their child can go to primary school. It is our believe that these aspects are underexposed in preconceptional counseling.

As we described in **Chapter 5** only 42 women got pregnant after KT at the Erasmus MC, in **Chapter 6** we identified that the total group of women who were transplanted at the age of 45 or younger comprised 350 women. This suggests that the incidence of pregnancy in this group rather low (12%). To explore motives for and against pregnancy, together with psychosocial and medical factors involved in decision making, we performed a mixed-method study. We performed in depth interviews in KT-recipients who had pregnancies after KT (P-group) and KT-recipients who were not pregnant after KT (NP-group). In both groups KT-recipients experienced a high threshold to discuss their pregnancy wish with their nephrologist. The nephrologists' advice played an important role in decision-making, but differed between the groups. In the P-group, a desire for autonomy and positive role models were decisive factors in proceeding with their pregnancy wish. In the NP-group, disease burden and risk perception were decisive factors in not proceeding with their pregnancy. Furthermore, we identified that women who became pregnant after KT were generally healthier than those who did not. Furthermore, nephrologists played a crucial role in both groups but differed in their attitude towards pregnancy after KT. One of the most striking findings was that, even nowadays when patients are more empowered than ever before, patients were still reluctant to discuss their pregnancy wish with their nephrologist.

As described in **Chapter 6** women reported different attitudes of nephrologists towards pregnancy and experienced a high threshold to discuss their pregnancy wish with their nephrologist. Llittle is known about how pre-pregnancy counseling after KT is conducted, especially among patients with risk factors for adverse outcomes. Therefore we conducted a cross-sectional web-based survey among nephrologists and gynaecologists in the Netherlands between March 2020 and February 2021 described in **Chapter 7**. It consisted of five clinical vignettes based on known risk factors for APO and questions on pre-pregnancy counseling in general. Per vignette, positive versus negative attitudes towards pregnancy and estimation of outcomes were examined. In total 52 (68%) nephrologists and 25 (32%) gynaecologists participated, of which 43 (56%) work in a university hospital. One third had no experience in this field. 63% of participants felt large responsibility for the decision

to become pregnant after KT. All gave a positive pregnancy advice in the vignette with ideal circumstances after KT (V1), versus 83% in V2 (proteinuria), 81% in V3 (proteinuria), 71% in V4 (combined risk factors). Only 2% of participants were positive in V5 (worst-case vignette). Chance of preeclampsia was underestimated by 89% in V1. Risk for graft loss was overestimated by 74% in V4 and 63% in V5. Counseling differed significantly between gynaecologists and nephrologists. Pregnancy outcomes after KT are not always estimated correctly by professionals which might be due to low exposure. Therefore, referral to expert care centers needs to be considered where counseling can be performed by a nephrologist and a gynaecologist together.

PART III

In **Chapter 8** we described the outcomes of pregnancy after living kidney donation (LKD). After LKD, glomerular filtration rate is reduced. Literature on the effect of pregnancy on long-term outcome after LKD is scarce. For counseling it is of great importance to know if pregnancy after LKD affects long-term outcomes of the mono-kidney and the mother. A retrospective multicenter study was performed in women who donated their kidney at a fertile age between 1981 and 2017. During (bi) annual visits, eGFR, blood pressure (BP), proteinuria, and cardiovascular events (CVE's) were measured. Pregnancies were recorded by interviews. Long-term outcomes after LKD and mean eGFR slope of women with pregnancies after LKD were compared to women who were pregnant before LKD or nulliparous. Pregnancy outcomes after LKD were compared with pregnancy outcomes before LKD. All analyses were multilevel and adjusted for baseline differences. 234 women were included; 43 nulliparous women, 142 women with 311 pregnancies before LKD, 26 women with 40 pregnancies after LKD and 18 women with 52 pregnancies before and after LKD. Median follow-up time after LKD was 12 years (IQR 7). No difference in mean eGFR before and after pregnancy after LKD was observed ($p = 0.13$). eGFR, BP, proteinuria, and CVE's after LKD were not significantly different in women with pregnancies after LKD compared to women who were pregnant before LKD or nulliparous. Hypertensive disorders of pregnancy occurred more often in pregnancies after LKD versus pregnancies before LKD (OR 4.19, 95% CI 1.70 – 10.35, $p = 0.002$). Pregnancy after LKD was not associated with adverse fetal outcomes. Our data demonstrates that, despite a higher incidence of hypertensive disorders, pregnancy after LKD did not have an effect on long-term outcomes, in particular change in eGFR. Therefore, a pregnancy wish alone should not be a reason to exclude women for LKD. Women with high BMI and hypertension are more at risk to have adverse pregnancy and LKD outcomes and should be counseled properly.

Conclusions

The studies in this thesis show that pregnancy outcomes after kidney transplantation are generally good. Pregnancy has no significant effect of pregnancy on eGFR after pregnancy and the risk of graft loss after pregnancy is not higher than graft loss in matched nulliparous kidney transplant recipients. Although these results are reassuring, a kidney transplant has a certain expiration date and kidney transplant recipients might be on dialysis or re-transplanted when their child is of school age. This is important information for pre-pregnancy counseling. Furthermore in interviews we identified that kidney transplant recipients experience a high threshold to discuss their pregnancy wish with their nephrologist. As incidence of pregnancy after KT is quite low, pregnancy outcomes after KT are not always estimated correctly by nephrologists and gynaecologists. Finally we demonstrated that pregnancy after KT has no effect on long term mono-kidney outcomes. There is a higher incidence of hypertensive disorders of pregnancy after LKD but no higher incidence of fetal outcomes compared to pregnancies prior to LKD.

Chapter 10

General Discussion

General Discussion

One of the main goals of this thesis was to obtain insight into the current pregnancy outcomes after kidney transplantation (KT) and kidney donation. In this thesis we describe the outcomes of pregnancy after KT for the mother, the kidney graft and the child. Furthermore we studied current pre-pregnancy counseling from the point of view of the kidney transplant recipient (KT-recipients) and the transplant professional. In the last part we describe the outcomes of pregnancy outcomes after living kidney donation (LKD), for the mother, the remaining kidney and the child.

Risk for graft loss after pregnancy

Our meta-analysis, described in **Chapter 2,** added more than 500 women from 23 additional studies to the literature since the last meta-analysis from 2011 by Deshpande on the subject which included 50 studies[1]. We report slightly higher numbers of graft loss within 2 years (9,4% versus 8%), and higher numbers of graft loss after 5 to 10 years post pregnancy(22,3% versus 19%) . Our outcome of graft loss of 38.5% more than 10-year postpartum is based on a pooled incidence of 5 new studies [2-6].

An important addition that was not covered in the previous meta-analysis was that we added 10 studies that compared the result of graft loss after KT with a nulliparous KT control group[2-5,7-12]. The absence of a difference in graft loss between parous and nulliparous is reassuring. Although the control groups were heterogenic, almost all studies were matched for age and SCr before conception. The question remains whether the control groups used are really comparable, because the reason that KT-recipients in control groups did not conceive might be the result of other underlying conditions, which can also influence graft loss.

Unfortunately, the number of years of follow-up after transplantation are rarely reported, which makes it hard to compare our graft loss numbers with the registries. The incidence of graft loss after KT in the Eurotransplant registry (age 16-34 years) was higher than, the number of graft loss after pregnancy in our meta-analysis. [13].

In addition to this meta-analysis we performed a single center study on graft loss and patient survival after delivery, which is described in **Chapter 5**. In this rather small population (n = 42) we discovered that 40% of the females lost their graft within 10 years after KT. This is still better than in the general kidney transplant population of the Erasmus MC [14]. However, the issue addressed here is that although graft loss is not more frequent after pregnancy, it is still the case that more than 40% of KT-recpients will return to dialyses or will need a re-transplant while their child is still young. Furthermore 12% of these women did not see their child reach adulthood, which means that from the child's perspective they lose their mother at

a very young age. These three aspects are underexposed in current literature and reviews on counseling issues, in which the focus is more on the pregnancy itself than the following period (after delivery) where the mother still has a 'chronic' condition[15]

In **Chapter 6** we performed qualitative research on experiences of KT-recipients with motherhood . KT-recipients who got pregnant after KT reported experiencing the same difficulties as most families with young children experience. However, compared to mothers without a chronic condition they must also deal with additional challenges and limitations, resulting from the renal replacement treatment and fear of health loss. Yoshikawa and colleagues concluded that these additional considerations and limitations do not seem to affect the quality of life in this group [16]. Whether being able to have children or not contributes to a higher or lower QoL after KT requires further investigation [17,18].

Effect of pregnancy on kidney function after kidney transplantation

In our meta-analyses we only found a small, but significant, rise in SCr within 2 years after delivery (87 KT-recipients derived from 3 studies[6,19,20]). This might be caused by restart of medication such as ACE inhibitors. On the other hand, this could have been the result of high rate of risk factors in the study population (65.9% hypertension, 36.5% SCr >1.5mg/dL prior to pregnancy), which makes these women more prone for deterioration of graft function or even graft loss[6]. Most importantly, in our meta-analysis we did not find an increase in SCr during the period 5 years after pregnancy. However, women with a malfunctioning graft or that are lost to follow-up are not present at longer times after pregnancy, possibly inducing bias. This is in line with the recent systematic review on the effect of pregnancy in chronic kidney disease, which reported no shift in CKD stage after pregnancy[21]. In line with the meta-analysis of **Chapter 2** we did observe a small decline our national PARTOUT dataset after first pregnancy, although this was not significant (p=0.08). That this decline was not significant in contrast to the meta-analysis might be caused by lower numbers of KT-recipients included. Furthermore, we used multiple eGFR measurements and a multilevel method. We observed a (non-significant) decline in mean eGFR of approximately 3 ml/min/1.73m^2 after first pregnancy (adjusted for transplant vintage and multiple measurements per women). Mean adjusted eGFR was not different after second and third pregnancy. This can be explained by the fact that most women in our study only had one pregnancy after KT. It is likely that, if complications occurred during this pregnancy, or if their kidney function had decreased, these women decided not to become pregnant again. Furthermore, 10 KT-recipients were pregnant again very soon after their first delivery, therefore no eGFR's of these

KT-recipients could be included for the period between first and second pregnancy or end of follow-up.
Furthermore women who had no physiological rise of eGFR during pregnancy had worse graft survival after delivery than women with an increase of eGFR during pregnancy. This absence of midterm hyperfiltration as a marker of renal reserve might be considered as a risk factor for long-term graft loss in addition to traditional risk factors.

Pregnancy outcomes after Kidney Transplantation

The pregnancy outcomes after KT of our national dataset were described in **Chapter 4.** This study includes 288 pregnancies and is the first and largest study to show pregnancy outcomes after KT per pre-pregnancy eGFR-categories including women with poor kidney function. Although pregnancy after KT remains high risk, the majority of pregnancies are successful (**Table 1**).

The fetal and maternal outcomes of our study are largely consistent with previous studies on pregnancy after KT[1,22]. However, when comparing CKD women with KT-recipients stratified per pre-pregnancy eGFR category, the incidence of preterm birth and low birth weight was higher in KT-recipients[23]. One study described similar outcomes, but this study did not systematically examine pre-pregnancy eGFR, which might lead to a possible underestimation of CKD stage resulting from the physiological eGFR rise in early pregnancy[21,24,25]. The physiological rise in serum creatinine in the third trimester is hard to distinguish from preeclampsia, especially when a women has pre-existent hypertension and proteinuria and can thereby lead to iatrogenic preterm birth [26]. The differences in the incidence of pre-term deliveries can thereby be explained by the variation in gynaecologists threshold for iatrogenic preterm delivery.

The absence of mid-term SCr dip and mid-term MAP dip indicating a lack of mid-term hyperfiltration is associated with adverse pregnancy outcomes. Midterm hyperfiltration reflects the functional reserve capacity of the kidney graft and the ability of vascular adaptation to the pregnancy. The association with a lack of midterm hyperfiltration and adverse pregnancy outcomes is independent pre-pregnancy eGFR. Earlier research in the healthy population and the pregnant chronic kidney disease (CKD) population showed a correlation between the degree of kidney dysfunction and/or the lack of hemodynamic adaptation and poor pregnancy outcomes[23,26-31] .

Table 1: Pregnancy Outcomes PARTOUT dataset, 288 pregnancies

Variable	eGFR ≥ 90 ml/min/1.73m² *N = 23*	eGFR 89 – 60 ml/min/1.73m² *N = 104*	eGFR 59 – 45 ml/min/1.73m² *N = 72*	eGFR 44 – 30 ml/min/1.73m² *N = 44*	eGFR <30 ml/min/1.73m² *N = 10*
Neonatal outcomes					
Gestational age, days (SD) **Gestational age, weeks**	264 (18) 37.7	253 (27) 36.1	244 (32) 34.9	241 (33) 34.4	221 (32) 31.6
Preterm birth <37 weeks*	7/21 (33%)	40/99 (40%)	40/70 (57%)	26/42 (62%)	10/10 (100%)
Preterm birth <34 weeks	2/7 (29%)	14/40 (35%)	22/40 (55%)	17/26 (65%)	7/10 (70%)
Birth weight, gram (SD)	2846 (753)	2512 (724)	2388 (940)	2087 (937)	1335 (725)
Birth weight < 2500 gram*	6/21 (29%)	42/96 (44%)	32/69 (46%)	28/41 (68%)	10/10 (100%)
Small for gestational age <p10	8/21 (38%)	33/91 (36%)	25/65 (39%)	21/40 (53%)	7/10 (70%)
NICU admission	2/23 (9%)	8/104 (8%)	9/72 (13%)	5/44 (11%)	4/9 (44%)
Stillbirth	0	4/103 (4%)	6/71 (8%)	4/44 (9%)	0
Neonatal mortality (in first 7 days of life)	1/23 (4%)	1/97 (1%)	2/64 (2%)	1/38 (3%)	2/9 (22%)
Maternal outcomes					
Gestational hypertension	6/17 (35%)	42/86 (49%)	39/63 (62%)	23/39 (59%)	4/6 (67%)
Pre-eclampsia	7/18 (39%)	33/85 (39%)	21/67 (31%)	13/40 (33%)	8/8 (100%)
Use of calcineurine inhibitor during pregnancy	6/21 (29%)	43/100 (43%)	40/71 (56%)	32/44 (73%)	6/10 (60%)

Incidences are shown as numerator/denominator(frequency, 95% CI) of pregnancies with available composite outcome data. Not all pregnancy outcomes were available for every patient. For categorical variables, incidences are shown as numerator/denominator, for continuous variables the number of complete cases are described here: *gestational age, n = 265. Percentile corrected for gestational age, n = 243*

Variables that are part of the composite outcome are marked with an asterisk. eGFR calculated with the CKD-EPI method, categories corresponding to Chronic Kidney Disease stages

Decision making and experiences of KT-recipients, nephrologists and gynaecologists, lessons learned

In **Chapter 6** we identified that women who became pregnant after KT were generally healthier than those who did not. During the interviews we identified that impaired health is also an important reason for women not to pursue pregnancy. Women who decided not to get pregnant experienced a higher disease burden than the group who did became pregnant, they were more focused on minimizing risks and preventing poor outcomes. Furthermore, they looked further than the pregnancy itself, they thought more about their ability to raise a child, as well as the impact on the graft, child and partner. Arguments for pregnancy were positive role models, desire for normality and autonomy. It is a known effect that individuals who are more autonomous and want to pursue desirable outcomes are most inspired by positive role models [32]. Women were striving for normality and felt that being able to bear children made them feel closer to normality. This phenomenon was also described in a study in which women described their chronic illnesses as deviations from normality and their pregnancies brought them closer to normality [33].

Nephrologists played a crucial role in decision making on pregnancy in KT-recipients who were pregnant and KT-recipients who did not became pregnant. Also, the attitude towards pregnancy after KT differed between nephrologists. Furthermore women reported feeling defeated by all the negative information they received from the nephrologist. And even now at a time when patients are more empowered than ever before, patients in our study still experienced reluctance to discuss their pregnancy wish with their nephrologist. The fact that the incidence of pregnancy after KT is low (12%) and more than 30% of the clinicians reported to have no experience with pregnancy after KT might be an explanation. A previous study regarding fertility care among CKD-patients showed that the amount of fertility care that was given was positively related with the amount of knowledge of clinicians on fertility care [34]. From this study, it can be hypothesized that with little experience, a clinician might be less attentive to the subject of pregnancy after KT in daily practice. When experience is lacking, clinicians need to fall back on guidelines and consensus statements. Unfortunately, these guidelines and consensus statements apply only to KT-recipients with excellent kidney function and no proteinuria and can perhaps better be enhanced by experienced clinicians[35,36]. This makes it difficult to counsel a patient with a bit of proteinuria or a slightly worse kidney function.

In **Chapter 7** we focused on the decision-making and the counseling process of the nephrologist and the gynaecologist. Both groups ranked kidney function, proteinuria and blood pressure as the three main factors for counseling and for risk identification. This matches current literature and guidelines [1,35-37]. Remark-

ably, gynaecologists scored 'a history of rejection' significantly more important than the nephrologist did. The chance of pre-eclampsia and preterm birth < 37 weeks was underestimated by the clinicians when compared to the PARTOUT-dataset described in **Chapter 4**. However, when we compared the clinicians estimates to an earlier study by Stoumpos et al (2016) KT-recipients with eGFR > 45 ml/min/1.73m2 showed 26% chance of pre-eclampsia-, the clinicians' estimation was adequate. The general chance of preterm birth found by Stoumpos et al (61%) was similar to our PARTOUT-findings described in **Chapter 4** [12]. Pregnancy outcomes of KT-recipients with pre-pregnancy eGFR > 90 ml/min/1.73m2 can be compared to the results of Piccoli et al, which show an incidence of preterm birth of 46% in pregnancies after KT in CKD-stage 1 (eGFR >90 mmol/L)[38]. Combining these previous studies and the PARTOUT-data, the estimation of birthweight remains underestimated by participants. Furthermore, there was an overestimation for the risk of graft loss within two years after delivery compared to the PARTOUT-set described in **Chapter 4**. As the PARTOUT dataset described in **Chapter 4** is the best reflection of the current pregnancy outcomes after KT in the Netherlands, this was not published at the time we send these questionnaires. Therefore it might be possible that clinician based there estimations on other (published) cohorts. This shows the need for publication of more elaborate data on pregnancy outcomes after KT.

In general, the majority of the clinicians had a positive attitude towards pregnancy after KT. This is in contrast to two surveys performed among KT-recipients on the counseling they actually received. In these studies, respectively one third and one fourth of the female KT-recipients said to have been counselled against pregnancy[39,40]. While it is not possible to know what the arguments of these doctors were, it is clear that their opinion counts and that the negative information can be overwhelming for women. Wiles et al also investigated pre-pregnancy counseling in CKD patients. They found that the doctors' positive or negative attitude towards a pregnancy had influence on the decision to become pregnant. The communication of risks can reduce the incidence of complications, if women choose not to become pregnant. [41]. These studies show the influence of the doctors' attitude, both positive and negative, on decision making in pre-pregnancy counseling after KT. In **Table 2** we propose some essential issues for counseling, derived from this thesis.

Table 2: Essential issues for counseling, extracted from this thesis

Will I lose my kidney sooner when I get pregnant after kidney transplantation?	*Women do not lose their kidney sooner because of pregnancy but there is a chance that kidney transplant recipients lose their graft when their child is still young. It is important for counseling to include the period after delivery*
Will a pregnancy after kidney transplantation effect my kidney function?	*Pregnancy did not have an additional effect on eGFR. After first pregnancy the kidney function was slightly lower which was not significant. Pregnancy does not seem to have an effect on eGFR after second and third pregnancies.*
What are the pregnancy outcomes after KT?	*Overall obstetric outcomes in KT-recipients are positive with a live birth rate of 93%, mean gestational age of 35+4 weeks and a mean birth weight of (2383 (SD 885) gram. Pregnancy outcomes sorted per pre-pregnancy eGFR-category are helpful for individualized pre-pregnancy counseling* ***(Table 1).***
What is the effect of pregnancy on the mono-kidney after living kidney donation	*Pregnancy after living kidney donation has no effect on kidney function.*
What are the pregnancy outcomes after living kidney donation	*Pregnancies after living kidney donation are more often complicated by hypertensive disorders of pregnancy, but have no more adverse fetal outcomes.*

Pregnancy after Living kidney donation

The eGFR after living kidney donation(LKD) was not different in women with or without a pregnancy after LKD. That is a reassuring message, when counseling women with a wish for children, who consider to become a live kidney donor. Even more reassuring is that we demonstrated, for the first time, that the eGFR slope after pregnancy was not different from the eGFR slope before pregnancy in LKD. In an earlier study in the general population, a similar non- negative effect of hypertensive disorders of pregnancy (HDP) was shown on kidney function after pregnancy [42].

We conclude that, despite a higher incidence of HDP, pregnancy after LKD does not affect long-term outcomes, especially not renal function. We know from earlier studies that women with preeclampsia are more at risk for hypertension and cardiovascular events later in life [43,44]. We did not observe this phenomenon in our data, this might be explained from the fact that most of our post-LKD pregnancies had a late onset mild preeclampsia and none of the women who were pregnant after LKD had a cardiovascular event. Of note that these women had a rather short follow-up time (median 11 years after pregnancy) and in literature cardiovascular events occur at longer periods of time after preeclampsia [43,44].

In line with earlier studies we also demonstrated a higher risk of preeclampsia and HDP after LKD [45,46]. Especially the studies from Norway and South Korea report

a lower incidence of gestational hypertension after LKD than our study [45,47]. The incidence of preeclampsia was in line with earlier studies, only the South Korean study reported a lower incidence[47]. Comparing these study outcomes remains difficult as studies use different definitions for gestational hypertension and preeclampsia.

BMI and BP before LKD were associated with adverse pregnancy outcomes. It can be hypothesized that women with a high BMI have smaller residual capacity of the mono-kidney after LKD and therefore are at higher risk for hypertension and HDP, as was suggested in an earlier letter [48]. Furthermore, women with high BMI and higher BP before LKD are at higher risk of hypertension and cardiovascular events after LKD. In studies in the general LKD population, hypertensive donors had no increased risk for reduced eGFR, proteinuria or ESRD in donors compared to donors without hypertension [49]. The same study group explored the risk of obese donors in a recent study on outcomes after LKD in the non-obese LKD population, where they did not find an increased risk of CVE or ESRD [50]. In contrary, the group of Locke did find a higher risk of mortality and ESRD in obese donors compared to non-obese donors [51,52]. More research is clearly necessary, but these data provide important information for counseling overweight women with a future pregnancy wish who want to donate their kidney.

Future Perspectives (Table 3)

Future Research

Although this thesis provides us with valuable information on several aspects on pregnancy after KT, there are still remaining research questions that have not been addressed in the current studies.

A logical next step would be to design prospective follow-up studies on pregnancy after KT. This could be facilitated by the PARTOUT-network, although due to the low incidence a larger network would be better. Thus collaboration between several registries in order to collect a larger amount of data would be off great value.

A start of a European network to gather more information on pregnancy after KT on a larger scale was made in the form of the 'CRISTEL-network' (Creation of a European RegIStry for Transplanted women Expecting a baby: a Longitudinal approach).

In this prospective cohort the following clinical questions could be investigated :

The effect of the immune status of the KT-recipients can be studied more accurately, it is then possible to systematically include donor specific HLA antibodies, HLA antibodies in general and HLA mismatches [53,54]. Furthermore, the type of (biopsy proven) rejection can be registered more accurately, this can make it possible to investigate if KT-recipients who received their kidney from their partner

have more rejection after pregnancy. Furthermore, it can be studied if the immune status has an effect on pregnancy outcomes such as pre-term birth and birthweight. It could well be that placentation between 8-16 weeks is less well accommodated in women with a less favorable immune status.

The study by Koenjer with data from the PARTOUT dataset showed no effect of vol (CNI) on pregnancy outcomes, but this might be caused by bias as the data were collected retrospectively [55]. To date no prospective studies have been performed on dosing tacrolimus during pregnancy after KT. Throughout gestation, maintaining tacrolimus target concentrations is complicated by physiological changes during pregnancy (e.g. hemodilution and drug metabolism) affecting tacrolimus' absorption, distribution, and metabolism.[56]. The ideal levels of tacrolimus in pregnancy are unknown. Too low levels might increase the risk for the graft, two high levels increase the risk for hypertension, kidney function decline and thrombotic microangiopathy in pregnancy. Therefore, a new multicenter project has started on pharmacokinetics of tacrolimus during pregnancy.

A recent paper by Feyaerts demonstrated that the maternal peripheral, uterine, and neonatal immune system development is dysregulated in KT-recipients, with effects of immunosuppressive medication especially calcine urine inhibitors. This could have important consequences for adverse short- and long-term health outcomes in the offspring[57]. A few heterogenic studies have been performed on the outcomes of children after KT. No increased risk of an abnormal concentration of urea, creatinine, sodium, and potassium was observed in newborns from KT-recipients [58]. Contradictory results on the effect of the immune status were reported. The concentration of IgG or IgM in children born to kidney transplant recipients was not different than in the control group[59]. However, a study by Ono demonstrated that children born from KT-recipients had a higher risk of hospital admission in the first months of life than those born to healthy women [60]. Various research questions about children born from KT-recipients remained unaddressed in the current literature. Ofcourse studies in children born from KT-recipients are difficult in terms of long-term (until young adulthood) follow-up and the need for a matched control group. There is a need for long-term prospective follow up of the children born from KT-recipients evaluating both (reno)vascular and immunological effects on these children.

As stated earlier a substantial part of the preterm deliveries could be considered as iatrogenic. This can be because it is hard for the clinician to distinguish the physiological rise in serum creatinine in the third trimester from preeclampsia especially when a women has pre-existent hypertension and proteinuria and can thereby lead to iatrogenic preterm birth [26]. When a proper biomarker of placental dysfunction can

be identified it might be possible to better differentiate and, in some cases, delay delivery [61]. Which may lead to better pregnancy outcomes.

Transplant Professionals

It is important to lower the threshold to discuss pregnancy after KT. Professionals must be aware of this problem and be proactive as women may not initiate this conversation themselves. Counseling must include the pros and cons and support well-informed decision-making [62]. Additionally, the long-term prognosis after pregnancy, the risk of graft failure, raising a child while being on dialysis, the risk of death must be discussed.

As described in **Chapter 7** gynaecologists and nephrologists might have a different decision-making process, therefore joint counseling can be considered. A recent Dutch guideline was developed on CKD and pregnancy[63]. Although the major part of this guideline is on pregnancy in CKD patients who are not transplanted (yet) pregnancy and CKD. the recommendations for centralized care in centers with experienced nephrologists and gynaecologists also counts for KT-recipients.

There is a need for guidelines on pregnancy and having children after KT, that could help clinicians to have a clear and consistent message regarding parenthood after transplantation and will help in uniform reproductive care for KT-recipients and kidney donors.

Kidney Transplant Recipients

It is not always clear to KT-recipients what the risks and possibilities are regarding pregnancy after KT. To promote equal access, there is a need for accurate and standardized educational materials on becoming pregnant and having a child after KT and the implications thereof. Educational materials for KT-recipients can be supplied by the hospital home monitoring app or patient federations. Such an e-learning on sexuality and pregnancy after transplantation is currently being developed for transplant professionals and transplant recipients by the European Society for Organ Transplantation.

Peer support programs may be beneficial for women considering pregnancy after KT. Peer support programs have been implemented amongst chronic illness patients with good results [64-66]. The extent to which peer support programs are useful and effective in this population does require further investigation.

Table 3: Future perspectives

Future research
What are the short and long-term health consequences for children born from kidney transplant recipients? What is the optimal dose of immunosuppressive medication in pregnant kidney transplant recipients? What is the effect of HLA sensibilisation of the kidney transplant recipient on the pregnancy and on the chance of rejection after pregnancy? How can we better differentiate between superimposed pre-eclampsia and kidney disease?
Transplant professionals
Try to lower the threshold to discuss a pregnancy wish. Include raising children while having a 'chronic condition' in counseling Consider joint pre-pregnancy counseling, nephrologist and gynecologist together Centralize (pre) pregnancy care in experienced academic centers
Kidney Transplant Recipients
Provide education materials on pregnancy and raising children after kidney transplantation Education materials can be supplied through home monitoring app and/or patient federations Initiate peer support programs

References

1. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant.* 2011;11(11): 2388-2404.
2. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J Am Soc Nephrol.* 2009;20(11): 2433-2440.
3. Rahamimov R, Ben-Haroush A, Wittenberg C, et al. Pregnancy in renal transplant recipients: long-term effect on patient and graft survival. A single-center experience. *Transplantation.* 2006;81(5): 660-664.
4. Sturgiss SN, Davison JM. Effect of pregnancy on the long-term function of renal allografts: an update. *Am J Kidney Dis.* 1995;26(1): 54-56.
5. Svetitsky S, Baruch R, Schwartz IF, et al. Long-Term Effects of Pregnancy on Renal Graft Function in Women After Kidney Transplantation Compared With Matched Controls. *Transplant Proc.* 2018;50(5): 1461-1465.
6. Keitel E, Bruno RM, Duarte M, et al. Pregnancy outcome after renal transplantation. *Transplantation Proceedings.* 2004;36(4): 870-871.
7. First MR, Combs CA, Weiskittel P, Miodovnik M. Lack of effect of pregnancy on renal allograft survival or function. *Transplantation.* 1995;59(4): 472-476.
8. Fischer T, Neumayer HH, Fischer R, et al. Effect of pregnancy on long-term kidney function in renal transplant recipients treated with cyclosporine and with azathioprine. *Am J Transplant.* 2005;5(11): 2732-2739.
9. Pour-Reza-Gholi F, Nafar M, Farrokhi F, et al. Pregnancy in kidney transplant recipients. *Transplant Proc.* 2005;37(7): 3090-3092.
10. Kashanizadeh N, Nemati E, Sharifi-Bonab M, et al. Impact of pregnancy on the outcome of kidney transplantation. *Transplant Proc.* 2007;39(4): 1136-1138.
11. Kim HW, Seok HJ, Kim TH, Han DJ, Yang WS, Park SK. The experience of pregnancy after renal transplantation: pregnancies even within postoperative 1 year may be tolerable. *Transplantation.* 2008;85(10): 1412-1419.
12. Stoumpos S, McNeill SH, Gorrie M, et al. Obstetric and long-term kidney outcomes in renal transplant recipients: a 40-yr single-center study. *Clin Transplant.* 2016;30(6): 673-681.
13. Eurotransplant. 2018.
14. Hol-Laging. *Clinical and Socioeconomic Aspects of Kidney Transplantation* [Doctoral thesis, Erasmus University Rotterdam, The Netherlands]2017.
15. Chittka D, Hutchinson JA. Pregnancy After Renal Transplantation. *Transplantation.* 2017;101(4): 675-678.
16. Yoshikawa Y, Uchida J, Akazawa C, Suganuma N. Associations between physical and psychosocial factors and health-related quality of life in women who gave birth after a kidney transplant. *Int J Womens Health.* 2018;10: 299-307.
17. Wei TY, Chiang YJ, Hsieh CY, Weng LC, Lin SC, Lin MH. Health related quality of life of long-term kidney transplantation recipients. *Biomed J.* 2013;36(5): 243-251.
18. Dobbels F, De Bleser L, De Geest S, Fine RN. Quality of life after kidney transplantation: the bright side of life? *Adv Chronic Kidney Dis.* 2007;14(4): 370-378.

19. Candido C, Cristelli MP, Fernandes AR, et al. Pregnancy after kidney transplantation: high rates of maternal complications. *J Bras Nefrol.* 2016;38(4): 421-426.
20. Kwek JL, Tey V, Yang L, Kanagalingam D, Kee T. Renal and obstetric outcomes in pregnancy after kidney transplantation: Twelve-year experience in a Singapore transplant center. *J Obstet Gynaecol Res.* 2015;41(9): 1337-1344.
21. Piccoli GB, Cabiddu G, Attini R, et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. *J Am Soc Nephrol.* 2015;26(8): 2011-2022.
22. Shah S, Venkatesan RL, Gupta A, et al. Pregnancy outcomes in women with kidney transplant: Metaanalysis and systematic review. *BMC Nephrol.* 2019;20(1): 24.
23. Wiles K, Webster P, Seed PT, et al. The impact of chronic kidney disease Stages 3-5 on pregnancy outcomes. *Nephrol Dial Transplant.* 2020.
24. Davison JM. The effect of pregnancy on kidney function in renal allograft recipients. *Kidney Int.* 1985;27(1): 74-79.
25. Sturgiss SN, Dunlop W, Davison JM. Renal haemodynamics and tubular function in human pregnancy. *Baillieres Clin Obstet Gynaecol.* 1994;8(2): 209-234.
26. Lopes van Balen VA, van Gansewinkel TAG, de Haas S, et al. Maternal kidney function during pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2019;54(3): 297-307.
27. Page EW, Christianson R. The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy. *Am J Obstet Gynecol.* 1976;125(6): 740-746.
28. Williams D, Davison J. Chronic kidney disease in pregnancy. *Bmj.* 2008;336(7637): 211-215.
29. Macdonald-Wallis C, Tilling K, Fraser A, Nelson SM, Lawlor DA. Associations of blood pressure change in pregnancy with fetal growth and gestational age at delivery: findings from a prospective cohort. *Hypertension.* 2014;64(1): 36-44.
30. Gaillard R, Bakker R, Willemsen SP, Hofman A, Steegers EA, Jaddoe VW. Blood pressure tracking during pregnancy and the risk of gestational hypertensive disorders: the Generation R Study. *Eur Heart J.* 2011;32(24): 3088-3097.
31. Park S, Lee SM, Park JS, et al. Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of Gestational Hyperfiltration. *Clin J Am Soc Nephrol.* 2017;12(7): 1048-1056.
32. Lockwood P, Jordan CH, Kunda Z. Motivation by positive or negative role models: regulatory focus determines who will best inspire us. *J Pers Soc Psychol.* 2002;83(4): 854-864.
33. Tyer-Viola LA, Lopez RP. Pregnancy with chronic illness. *J Obstet Gynecol Neonatal Nurs.* 2014;43(1): 25-37.
34. van Ek GF, Krouwel EM, Nicolai MPJ, et al. What is the role of nephrologists and nurses of the dialysis department in providing fertility care to CKD patients? A questionnaire study among care providers. *Int Urol Nephrol.* 2017;49(7): 1273-1285.
35. McKay DB, Josephson MA. Reproduction and Transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. *American Journal of Transplantation.* 2005;5(7): 1592-1599.
36. Transplantation EEGoR. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant.* 2002;17 Suppl 4: 50-55.
37. van Buren MC, Schellekens A, Groenhof TKJ, et al. Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis. *Transplantation.* 2020;104(8): 1675-1685.

38. Piccoli GB, Cabiddu G, Attini R, et al. Outcomes of Pregnancies After Kidney Transplantation: Lessons Learned From CKD. A Comparison of Transplanted, Nontransplanted Chronic Kidney Disease Patients and Low-Risk Pregnancies: A Multicenter Nationwide Analysis. *Transplantation.* 2017;101(10): 2536-2544.
39. Rupley DM, Janda AM, Kapeles SR, Wilson TM, Berman D, Mathur AK. Preconception counseling, fertility, and pregnancy complications after abdominal organ transplantation: a survey and cohort study of 532 recipients. *Clin Transplant.* 2014;28(9): 937-945.
40. Humphreys RA, Wong HHL, Milner R, Matsuda-Abedini M. Pregnancy outcomes among solid organ transplant recipients in British Columbia. *J Obstet Gynaecol Can.* 2012;34(5): 416-424.
41. Wiles KS, Bramham K, Vais A, et al. Pre-pregnancy counseling for women with chronic kidney disease: a retrospective analysis of nine years' experience. *BMC Nephrol.* 2015;16: 28.
42. Paauw ND, van der Graaf AM, Bozoglan R, et al. Kidney Function After a Hypertensive Disorder of Pregnancy: A Longitudinal Study. *Am J Kidney Dis.* 2018;71(5): 619-626.
43. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet.* 2005;366(9499): 1797-1803.
44. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ.* 2007;335(7627): 974.
45. Reisæter AV, Røislien J, Henriksen T, Irgens LM, Hartmann A. Pregnancy and Birth After Kidney Donation: The Norwegian Experience. *American Journal of Transplantation.* 2009;9(4): 820-824.
46. Ibrahim HN, Akkina SK, Leister E, et al. Pregnancy outcomes after kidney donation. *American Journal of Transplantation.* 2009;9(4): 825-834.
47. Yoo KD, Lee H, Kim Y, et al. Maternal and fetal outcomes of pregnancies in kidney donors: A 30-year comparative analysis of matched non-donors in a single center. *Kidney Res Clin Pract.* 2018;37(4): 356-365.
48. Lely AT, van Londen M, Navis G. Gestational hypertension and preeclampsia in living kidney donors. *N Engl J Med.* 2015;372(15): 1468-1469.
49. Ibrahim HN, Hebert SA, Murad DN, et al. Outcomes of Hypertensive Kidney Donors Using Current and Past Hypertension Definitions. *Kidney Int Rep.* 2021;6(5): 1242-1253.
50. Ibrahim HN, Murad DN, Hebert SA, et al. Intermediate Renal Outcomes, Kidney Failure, and Mortality in Obese Kidney Donors. *J Am Soc Nephrol.* 2021;32(11): 2933-2947.
51. Locke JE, Reed RD, Massie AB, et al. Obesity and long-term mortality risk among living kidney donors. *Surgery.* 2019;166(2): 205-208.
52. Locke JE, Reed RD, Massie A, et al. Obesity increases the risk of end-stage renal disease among living kidney donors. *Kidney Int.* 2017;91(3): 699-703.
53. Zhang R. Donor-Specific Antibodies in Kidney Transplant Recipients. *Clin J Am Soc Nephrol.* 2018;13(1): 182-192.
54. Ahmed SB, Bentley-Lewis R, Hollenberg NK, Graves SW, Seely EW. A comparison of prediction equations for estimating glomerular filtration rate in pregnancy. *Hypertens Pregnancy.* 2009;28(3): 243-255.
55. Koenjer LM, Meinderts JR, van der Heijden OWH, et al. Comparison of pregnancy outcomes in Dutch kidney recipients with and without calcineurin inhibitor exposure: a retrospective study. *Transpl Int.* 2021;34(12): 2669-2679.

56. Le HL, Francke MI, Andrews LM, de Winter BCM, van Gelder T, Hesselink DA. Usage of Tacrolimus and Mycophenolic Acid During Conception, Pregnancy, and Lactation, and Its Implications for Therapeutic Drug Monitoring: A Systematic Critical Review. *Ther Drug Monit.* 2020;42(4): 518-531.
57. Feyaerts D, Gillard J, van Cranenbroek B, et al. Maternal, Decidual, and Neonatal Lymphocyte Composition Is Affected in Pregnant Kidney Transplant Recipients. *Front Immunol.* 2021;12: 735564.
58. Borek-Dziecioł B, Czaplinska N, Szpotanska-Sikorska M, et al. Selected Biochemical Parameters in Children of Mothers After Kidney Transplantation. *Transplant Proc.* 2020;52(8): 2294-2298.
59. Drozdowska-Szymczak A, Kociszewska-Najman B, Schreiber-Zamora J, et al. Evaluation of selected markers of the immune system in children of renal transplant recipients. *Transplant Proc.* 2014;46(8): 2703-2707.
60. Ono E, Dos Santos AM, Viana PO, et al. Immunophenotypic profile and increased risk of hospital admission for infection in infants born to female kidney transplant recipients. *Am J Transplant.* 2015;15(6): 1654-1665.
61. Bramham K, Seed PT, Lightstone L, et al. Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. *Kidney Int.* 2016;89(4): 874-885.
62. Snoek R, van der Graaf R, Meinderts JR, et al. Pregnancy in Advanced Kidney Disease: Clinical Practice Considerations on a Challenging Combination. *Nephron.* 2020;144(4): 185-189.
63. Dutch Multidisciplinary Guideline Pregnancy and Chronic Kidney Disease (NIV & NVOG). <**https://richtlijnendatabase.nl/richtlijn/zwangerschap_en_chronische_nierschade_cns/startpagina_-_zwangerschap_en_chronische_nierschade.html**> Published 2021. Accessed 01-12-2021 2021.
64. Dennis CL. Peer support within a health care context: a concept analysis. *Int J Nurs Stud.* 2003;40(3): 321-332.
65. Harris GE, Larsen D. HIV peer counseling and the development of hope: perspectives from peer counselors and peer counseling recipients. *AIDS Patient Care STDS.* 2007;21(11): 843-860.
66. Embuldeniya G, Veinot P, Bell E, et al. The experience and impact of chronic disease peer support interventions: a qualitative synthesis. *Patient Educ Couns.* 2013;92(1): 3-12.

Chapter 11

Nederlandse samenvatting

Samenvatting en conclusies

Het doel van dit onderzoek is om beter inzicht te krijgen in de huidige uitkomsten in Nederland voor moeder, kind & niertransplantatie. Zodat we de vragen rondom zwangerschap na niertransplantatie en nierdonatie kunnen beantwoorden. Dit is van belang omdat data en uitkomsten van zwangerschap na niertransplantatie nu vooral afkomstig zijn uit Amerika en deze niet altijd generaliseerbaar zijn naar onze Nederlandse populatie. Ook zijn deze databases gevuld met zelf gerapporteerde data door patiënten, wat de uitkomsten minder betrouwbaar maakt. Verder bestaat de literatuur vooral uit retrospectieve studies van kleine aantallen. Voor dit doel is het PARTOUT netwerk opgericht (Pregnancy After Renal Transplantation OUTcomes) om data te verzamelen van alle zwangerschappen na niertransplantatie in Nederland.

Deel I

In **Hoofdstuk 2** hebben we studies vergeleken die rapporteerden over transplantaatoverleving en invloed van zwangerschap op nierfunctie. Onze zoekstrategie leverden 38 studies op die rapporteerden over transplantaatoverleving na zwangerschap waarvan 10 studies met een controlegroep die niet zwanger werd. 18 studies rapporteerden over het effect van zwangerschap op nierfunctie (serum kreatinine). De samengevoegde incidentie van transplantaatverlies was 9.4% binnen 2 jaar na bevalling, 9.2% binnen 2-5 jaar, 22.3 tussen 5-10 jaar na bevalling en 38.5% > 10 jaar na bevalling. Uit de analyse blijkt dat de nierfunctie binnen twee jaar na bevalling lager is (0.18 mg/dL, 95% Confidence Interval (CI) [0.05-0.32], p = 0.01) dan voor de zwangerschap. In perioden langer na de bevalling was het verschil met de nierfunctie voor de zwangerschap niet significant verschillend meer. Verder zagen we geen verschil in transplantaatverlies bij vrouwen die zwanger werden na niertransplantatie vergeleken met vrouwen die niet zwanger werden na niertransplantatie. Uit de systematische review blijkt dat vooral proteïnurie voor de zwangerschap, hoge bloeddruk en slechte nierfunctie risico factoren zijn voor transplantaatverlies na zwangerschap. We concluderen uit deze meta-analyse dat er alleen een effect op nierfunctie gezien is kort na de bevalling, wat ook veroorzaakt kan worden door publicatie bias.
Vervolgens hebben we het PARTOUT netwerk opgericht om het effect van zwangerschap op nierfunctie en uitkomsten van zwangerschap na niertransplantatie te onderzoeken. De resultaten van deze twee multicenter cohort studies worden beschreven in **Hoofdstuk 3** en **Hoofdstuk 4**. **In Hoofdstuk 3** beschreven we de multi-

level analyse naar het effect van zwangerschap op nierfunctie na niertransplantatie. Het verloop van eGFR voor en na zwangerschap werd geanalyseerd door middel van generalized estimating equations (GEE) multilevel analyses gecorrigeerd voor meerdere metingen per vrouw en voor tijd na niertransplantatie. De vrouwen zijn hun eigen controlegroep. We includeerden 3194 eGFR metingen voor en na zwangerschap in 109 (55%) vrouwen met 1, 78 (40%) met 2, en 10 (5%) vrouwen met 3 zwangerschappen na niertransplantatie. De mediane follow-up na eerste bevalling na niertransplantatie is 14 jaar (interquartile range, 18 jaar). De gecorrigeerde gemiddelde eGFR voor zwangerschap was 59 ml/min/1.73m² (SEM (Standard Error of the Mean) 1.72; 95% confidence interval (CI), 56-63), na de eerste zwangerschap 56 ml/min/1.73m² (SEM 1.70; 95% CI, 53-60), na tweede zwangerschap 56 ml/min/1.73m2 en na de derde zwangerschap 55 ml/min/1.73m². In het geheel genomen is de eGFR achteruitgang na eerste, tweede en derde zwangerschap niet slechter dan voor de zwangerschap (p=0.28). Echter de gecorrigeerde gemiddelde eGFR na eerste zwangerschap was 2.8 mL/min/1.73 m² (p = 0.08) lager dan voor de zwangerschap. Ook is getest of zwangerschap een sneller verval van eGFR per jaar liet zien door middel van het toevoegen van de interactieterm: 'jaren na niertransplantatie*na zwangerschap'. Dit liet ook geen additioneel effect van zwangerschap op nierfunctie achteruitgang zien; na eerste zwangerschap (p = 0.29), na tweede zwangerschap (p = 0.08) en na derde zwangerschap (p = 0.39). We concluderen dat de eerste zwangerschap na niertransplantatie een klein maar niet significant effect heeft op de achteruitgang van nierfunctie. Vrouwen die tijdens de zwangerschap een verbetering hadden van nierfunctie (midterm hyperfiltratie) waren geassocieerd met betere eGFR en transplantaatoverleving na niertransplantatie. In **Hoofdstuk 4** beschrijven we de uitkomsten van zwangerschap in Nederland. Deze studie is ook gedaan met data uit de PARTOUT database. De uitkomsten zijn geanalyseerd per nierfunctie categorie. Om te identificeren wat de risicofactoren zijn van slechte zwangerschapsuitkomsten werd er een gecombineerd eindpunt vastgesteld. Geboortegewicht < 2500 gram, vroeggeboorte < 37 weeks, ernstige hypertensie in het 3e trimester, (SBP > 160 en/of DBP > 110 mmHg) en/of > 15% afname van serum creatinine tijdens de zwangerschap. 288 eenling zwangerschappen van 192 vrouwen werden geïncludeerd. In totaal werden 93% van de kinderen levend geboren, met een gemiddelde zwangerschapsduur van 35.6 weken, en een gemiddeld geboortegewicht van 2383 gram. Onafhankelijke risicofactoren voor slechte zwangerschapsuitkomsten waren slechtere nierfunctie voor de zwangerschap, procentuele daling van serum creatinine en van de mean arterial pressure; odds ratio's 1.01 (95% CI 1.00-1.02), 0.95 (0.91-0.98) and 0.94 (0.90 tot 0.98). Slechte zwangerschapsuitkomsten waren ook een significante risico factor voor transplantaatverlies (HR 2.55, 1.09 tot 5.96). Deze studie laat klinische en

nieuwe data zien van zwangerschapsuitkomsten na niertransplantatie per nierfunctie categorie. Dit maakt dat deze uitkomsten goed te gebruiken zijn voor counseling van niertransplantatie patiënten met een zwangerschapswens. Over het algemeen genomen waren de obstetrische uitkomsten goed. De zwangerschapsuitkomsten zijn met name afhankelijk van nierfunctie voor de zwangerschap en de mate van hemodynamische aanpassingen tijdens de zwangerschap.

Deel 2

Essentiële zaken voor pre-zwangerschapsbegeleiding zijn beschreven in **Hoofdstuk 5, Hoofdstuk 6** en **Hoofdstuk 7**. In **Hoofdstuk 5** en **Hoofdstuk 6** zijn alleen de data van het Erasmus MC beschreven. In **Hoofdstuk 5** analyseerden we de niertransplantatie overleving en de patiënten overleving na zwangerschap in het Erasmus MC. De mediane follow-upduur na de eerste bevalling was 12,5 jaar (spreiding: 1-34 jaar). Tijdens de follow-up overleden 5 (12%) van de vrouwen 1 tot 20 jaar na de bevalling (mediaan 6 jaar). De tienjarige transplantaatoverleving was 40%. Hoewel de overleving van patiënt en transplantaat na niertransplantatie in deze subgroep langer was dan in onze algemene niertransplantatie populatie, zag bijna een op de acht van deze vrouwen (12%) hun kind niet volwassen worden. In de algemene Nederlandse bevolking verliest slechts 3,9% van de kinderen een van hun ouders voordat ze volwassen zijn. Hoewel de transplantaatoverleving in deze subgroep beter was, zijn meer dan twee van de vijf van deze moeders (40%) weer aan de dialyse of hebben ze een nieuwe niertransplantatie nodig voordat hun kind naar de basisschool kan. Wij zijn van mening dat deze aspecten in pre-conceptionele counseling onderbelicht worden.

Zoals we in **Hoofdstuk 5** beschreven, werden in het Erasmus MC slechts 42 vrouwen zwanger na KT, in **Hoofdstuk 6** identificeerden we dat de totale groep vrouwen die op 45-jarige leeftijd of jonger getransplanteerd werd 350 vrouwen omvatte. Dit suggereert dat de incidentie van zwangerschap in deze groep vrij laag is (12%). Om motieven voor en tegen zwangerschap te onderzoeken, samen met psychosociale en medische factoren die een rol spelen bij de besluitvorming, hebben we een mixed-method studie uitgevoerd. We voerden diepte-interviews uit bij niertransplantatie patiënten die zwanger waren na niertransplantatie (P-groep) en niertransplantatie patiënten die niet zwanger waren na KT (NP-groep). In beide groepen ervaren niertransplantatie patiënten een hoge drempel om hun zwangerschapswens met hun nefroloog te bespreken. Het advies van de nefrologen speelde een belangrijke rol bij de besluitvorming, maar verschilde tussen de groepen. In de P-groep waren een verlangen naar autonomie en positieve rolmodellen beslissende factoren om aan hun zwangerschapswens te voldoen. In de NP-groep waren ziektelast en risico-

perceptie doorslaggevende factoren om de zwangerschap niet door te laten gaan. Verder hebben we vastgesteld dat vrouwen die zwanger werden na niertransplantatie over het algemeen gezonder waren dan degenen die dat niet deden. Bovendien speelden nefrologen in beide groepen een cruciale rol, maar verschilden ze in hun houding ten opzichte van zwangerschap na niertransplantatie. Een van de meest opvallende bevindingen was dat patiënten, zelfs nu, nog steeds terughoudend zijn om hun zwangerschapswens met hun nefroloog te bespreken.
Er is tot nu toe weinig bekend over hoe counseling voorafgaand aan de zwangerschap na niertransplantatie wordt uitgevoerd, vooral bij patiënten met risicofactoren voor nadelige uitkomsten. Daarom hebben we tussen maart 2020 en februari 2021 een cross-sectioneel web-based onderzoek uitgevoerd onder nefrologen en gynaecologen in Nederland, beschreven in **Hoofdstuk 7.** Het bestond uit vijf klinische vignetten op basis van bekende risicofactoren voor slechte zwangerschapsuitkomsten en vragen over zwangerschaps counseling bij niertransplantatie patiënten in het algemeen. Per vignet is gekeken naar positieve versus negatieve houdingen ten opzichte van zwangerschap en naar schatting van uitkomsten. In totaal deden 52 (68%) nefrologen en 25 (32%) gynaecologen mee, waarvan 43 (56%) werkzaam in een academisch ziekenhuis. Een derde had geen ervaring op dit gebied. 63% van de deelnemers voelde een grote verantwoordelijkheid voor de beslissing om zwanger te worden na niertransplantatie. Allen gaven een positief zwangerschapsadvies in het vignet met ideale omstandigheden na niertransplantatie (V1), versus 83% in V2 (proteinurie), 81% in V3 (hypertensie), 71% in V4 (gecombineerde risicofactoren). Slechts 2% van de deelnemers was positief in V5 (slechtste scenario vignet). De kans op pre-eclampsie werd in V1 met 89% onderschat. Het risico op transplantaatverlies werd overschat met 74% in V4 en 63% in V5. Counseling verschilde significant tussen gynaecologen en nefrologen. Zwangerschapsuitkomsten na niertransplantatie worden niet altijd correct ingeschat door professionals, wat te wijten kan zijn aan een lage blootstelling. Daarom adviseren wij om niertransplantatie met een zwangerschapswens te verwijzen naar centra met ervaren nefrologen en gynaecologen zodat ook de begeleiding gezamenlijk door de nefroloog en gynaecoloog kan worden uitgevoerd.

Deel 3

In **Hoofdstuk 8** beschreven we de uitkomsten van zwangerschap na levende nierdonatie (LKD). Na LKD wordt de glomerulaire filtratiesnelheid verminderd. Literatuur over het effect van zwangerschap op de lange termijn uitkomst na LKD is schaars. Voor counseling is het van groot belang om te weten of zwangerschap na LKD de lange termijn uitkomsten van de mononier en de moeder beïnvloedt. Een retrospec-

tieve multicenter studie werd uitgevoerd in de twee grootste levende nierdonatie centra in Nederland bij vrouwen die tussen 1981 en 2017 op vruchtbare leeftijd hun nier afstonden. Tijdens (twee)jaarlijkse bezoeken werden eGFR, bloeddruk, proteinurie en cardiovasculaire events gemeten. Zwangerschappen werden geregistreerd door middel van interviews. Langetermijn uitkomsten na LKD en eGFR-verloop van vrouwen met zwangerschappen na LKD werden vergeleken met vrouwen die zwanger waren vóór LKD of die nooit zwanger geweest waren. Zwangerschapsuitkomsten na LKD werden vergeleken met zwangerschapsuitkomsten vóór LKD. Alle analyses waren multilevel en gecorrigeerd voor baselineverschillen. 234 vrouwen werden geïncludeerd; 43 nulliparae vrouwen, 142 vrouwen met 311 zwangerschappen voor LKD, 26 vrouwen met 40 zwangerschappen na LKD en 18 vrouwen met 52 zwangerschappen voor en na LKD. De mediane follow-upduur na LKD was 12 jaar (IQR 7). Er werd geen verschil in eGFR-verloop voor en na de zwangerschap na LKD (p = 0.13). eGFR, BP, proteïnurie en cardiovasculaire events na LKD waren niet significant verschillend bij vrouwen met zwangerschappen na LKD in vergelijking met vrouwen die zwanger waren vóór LKD of nullipara. Hypertensieve aandoeningen tijdens de zwangerschap kwamen vaker voor bij zwangerschappen na LKD versus zwangerschappen vóór LKD (OR 4,19, 95% BI 1,70 – 10,35, p = 0,002). Zwangerschap na LKD was niet geassocieerd met nadelige foetale uitkomsten. Onze gegevens tonen aan dat, ondanks een hogere incidentie van hypertensieve aandoeningen, zwangerschap na LKD geen effect had op de langetermijnuitkomsten, met name verandering in eGFR. Een zwangerschapswens alleen mag daarom geen reden zijn om vrouwen voor LKD uit te sluiten. Vrouwen met een hoge BMI en hypertensie lopen meer risico op nadelige zwangerschaps- en LKD-uitkomsten.

Conclusies

De studies in dit proefschrift laten zien dat zwangerschapsuitkomsten na niertransplantatie over het algemeen goed zijn. Zwangerschap heeft geen significant effect van zwangerschap op eGFR na zwangerschap en het risico op transplantaatverlies na zwangerschap is niet hoger dan transplantaatverlies bij gematchte niertransplantatie ontvangers die niet zwanger werden. Hoewel deze resultaten geruststellend zijn, heeft een niertransplantatie een bepaalde houdbaarheidsdatum en kunnen ontvangers van een niertransplantatie moeten gaan dialyseren of opnieuw worden getransplanteerd wanneer hun kind nog jong is. Dit is belangrijke informatie voor zwangerschaps counseling. Verder hebben we in interviews vastgesteld dat niertransplantatiepatiënten een hoge drempel ervaren om hun zwangerschapswens

met hun nefroloog te bespreken. Aangezien de incidentie van zwangerschap na niertransplantatie vrij laag is, worden zwangerschapsuitkomsten na niertransplantatie niet altijd correct ingeschat door nefrologen en gynaecologen. Ten slotte hebben we aangetoond dat zwangerschap na niertransplantatie geen effect heeft op lange termijn mono-nier uitkomsten. Er is een hogere incidentie van hypertensieve aandoeningen van de zwangerschap na LKD, maar geen hogere incidentie van foetale uitkomsten in vergelijking met zwangerschappen voorafgaand aan LKD.

Chapter 12

Appendices

List of abbreviations

APO: Adverse Pregnancy Outcomes
B: Coefficient estimate
BMI: Body mass index
BP: Blood Pressure
cAPO: Combined adverse pregnancy outcome
CI: Confidence interval
CKD: Chronic kidney disease
CNI: Calcineurin inhibitors
CVE: Cardio Vascular Event
DBP: Diastolic blood pressure
DCGL: Death Censored Graft Loss
eGFR: estimated Glomerular Filtration Rate
ESRD: End Stage Kidney Disease
GEE: Generalized Estimating Equations
GFR: Glomerular Filtration Rate
GL: Graft Loss
HDP: Hypertensive Disorders of Pregnancy
HLA: Human Leucocyte Antigen
IQR: Inter quartile range
KT: Kidney Transplantation
KT-recipients: Kidney Transplant Recipients
LKD: Living Kidney Donation
MAP: Mean Arterial Pressure
NOTR: Dutch Organ Transplant Registry
OR: Odds ratio
PARTOUT: Pregnancy After Renal Transplantation OUTcomes
PE: Pre-eclampsia
PRA: Panel Reactive Antibodies
SBP: Systolic blood pressure
SCr: Serum Creatinine
SD: Standard Deviation
SEM: Standard error of the mean
TCI: Transplant to conception interval (years)
TPR: Transplant Pregnancy Registry

List of Publications

First author:

Van Buren MC, Massey EK, Maasdam L, et al. For Love or Money? Attitudes Toward Financial Incentives Among Actual Living Kidney Donors. American Journal of Transplantation. 2010;10(11): 2488-2492.

van Buren M, Lely T, van de Wetering J. Essential Issues for Pregnancy Counseling in Renal Transplant Women. *Transplantation.* 2018;102(6): e254.

van Buren MC, Schellekens A, Groenhof TKJ, et al. Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis. *Transplantation.* 2020;104(8): 1675-1685.

van Buren MC, Beck DK, Lely AT, van de Wetering J, Massey EK. EXPloring attitudes and factors influencing reproductive Choices in kidney Transplant patients (The EXPECT-study). *Clin Transplant.* 2021: e14473.

van Buren MC, Gosselink M, Groen H, et al. Effect of Pregnancy on EGFR After Kidney Transplantation: a National Cohort Study. *Transplantation*. 2022 Jun 1;106(6):1262-1270.

Co-author

Tielen M, van Exel NJA, **van Buren MC**, Maasdam L, Weimar W. Attitudes towards medication non-adherence in elderly kidney transplant patients: a Q methodology study. Nephrology Dialysis Transplantation. 2011;26(5): 1723-1728.

Beck D, Been-Dahmen J, Peeters M, Grijpma JW, van der Stege, H, Tielen M, **van Buren M**, Weimar W, Ista E, Massey E, van Staa. A Nurse-Led Self-Management Support Intervention (ZENN) for Kidney Transplant Recipients Using Intervention Mapping: Protocol for a Mixed-Methods Feasibility Study. JMIR Res Protoc. 2019;8(3): e11856.

Been-Dahmen JMJ, Beck DK, Peeters MAC, van der Stege, H, Tielen M, **van Buren M**, Ista E, Massey E, van Staa. Evaluating the feasibility of a nurse-led self-management support intervention for kidney transplant recipients: a pilot study. BMC Nephrol. 2019;20(1): 143.

Maasdam L, Timman R, Cadogan M, Tielen M, **van Buren MC**, Weimar W, Massey EK. Exploring health literacy and self-management after kidney transplantation: A prospective cohort study. Patient Educ Couns. 2022;105(2): 440-446.

Margriet E. Gosselink, **Marleen C. van Buren**, Judith Kooiman, et al. A nationwide Dutch cohort study shows relatively good pregnancy outcomes after kidney transplantation and finds risk factors for adverse outcomes. Kidney International, In Press, Journal Pre-proof, Available online 28 June 2022

About the Author

Marleen van Buren was born on July 1th 1981 in Schoonhoven, the Netherlands. After attending secondary education (HAVO) at the Willem de Zwijger in 1999 in Schoonhoven, she completed her bachelor of nursing at the Hogeschool Rotterdam and the Erasmus MC. Her graduation project was on developing clinical nursing guidelines for lung transplant recipients at the Pulmonary Department, where after she continued working as a registered nurse at the Erasmus MC. She continued training in intensive care nursing at the Maasstad Hospital in Rotterdam and afterwards worked there as an intensive care nurse. In 2008 she started the Master in Advanced Nursing Practice program at the Hogeschool Rotterdam and the Kidney Transplant Department of the Erasmus MC; after graduation in 2010 she continued working in this department as a registered Nurse Practitioner. In 2016 she started as a PhD candidate under the supervision of Prof. Dr. R. Zietse, Dr. J. van de Wetering and Dr. A.T. Lely. She co-initiated the national data network (Pregnancy After Renal Transplantation OUTcomes) PARTOUT together with both transplant and obstetric professionals.

She was a board member of the National Nurse Practitioner Society (V&VN VS) and chair of its congress committee. Currently she is the vice-chair of the European Transplant Allied Healthcare Professionals committee of ESOT. She enjoys educating obstetric and transplant nurses and medical students. She lives in Rotterdam with her husband Jubi and children, Jasmijn (2012) and Karel (2014).

Portfolio

ERASMUS UNIVERSITY ROTTERDAM
PHD PORTFOLIO

Marleen van Buren

Description	EC
Required	
Oral presentation European Society of Organ Transplantation(ESOT) congress Glasgow (2011)	0.50
European Society Organ Transplantation (ESOT) congress Glasgow (2011)	1.20
Oral presentation International Transplant Nurses Society (ITNS) congress, Gothenburg (2011)	0.50
International Transplant Nurses Society (ITNS) congress, Gothenburg (2011)	1.20
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), Maastricht (2012)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), Maastricht (2012)	0.75
Oral presentation The Transplantation Society (TTS) congress Berlin (2012)	0.50
Oral presentation The Transplant Society (TTS) congress Berlin (2012)	1.20
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), Leiden (2014)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), (2014)	0.75
Erasmus MC - ESP40 Case-control Studies (2015)	0.70
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), Groningen (2016)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), Groningen (2016)	0.75
Training Open Clinica (2016)	0.50
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), Utrecht (2017)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), Utrecht (2017)	0.75
Oral presentation European Society Organ Transplantation (ESOT) congress Barcelona (2017)	0.50
Oral presentation European Society Organ Transplantation (ESOT) congress Barcelona (2017)	0.50
European Society Organ Transplantation (ESOT) congress Barcelona (2017)	1.20
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), Rotterdam (2018)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), Rotterdam (2018)	0.75

Erasmus MC - ESP66 Logistic Regression (2018)	1.40
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), Amsterdam (2019)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), Amsterdam (2019)	0.75
Oral Presentation Ethical Legal and Psychosocial Aspects of Transplantation (ELPAT) congress, Krakov (2019)	0.50
Ethical Legal and Psychosocial Aspects of Transplantation (ELPAT) congress, Krakov (2019)	1.20
Oral presentation European Society Organ Transplantation (ESOT) congress Copenhagen (2019)	0.50
European Society Organ Transplantation (ESOT) congress Copenhagen (2019)	1.20
Erasmus MC - Biomedical English Writing and Communication (2020)	0.00
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), Roermond (2020)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), Roermond (2020)	0.75
Training Lime Survey (2020)	0.50
Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers) (2020)	1.50
Erasmus MC - Scientific Integrity (2020)	0.30
Oral presentation Annual scientific meeting of the Dutch Transplant Society (NTV), digital (2021)	0.50
Annual scientific meeting of the Dutch Transplant Society (NTV), digital (2021)	0.75
Optional	
Board member Dutch Nurse Practitioners Society (V&VN VS) (2015)	2.00
Teacher Minor "Organ Transplantation", master medical students (2020)	0.50
Board member European Transplant Allied Healthcare Professionals (ETAHP), section of ESOT (2020)	0.50
Supervision of Master Student (2021)	2.00
Teacher Obstetric Nurse Education, Erasmus Care Academy (2021)	3.00
Teacher Optional subject "Transplant Medicine", bachelor students (2021)	1.00
Vice chair European Transplant Allied Healthcare Professionals (ETAHP), section of ESOT (2021)	1.00
Co-founder & secretary of the Pregnancy after Renal Transplantation OUTcomes (PARTOUT) network (2021)	4.00
Total EC	------ + **39.60**