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Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis

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Background. The incidence of pregnancy in kidney transplantation (KT) recipients is increasing. Studies report that the incidence of graft loss (GL) during pregnancy is low, but less data are 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 postpartum. 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 2 years after pregnancy, 9.2% within 2–5 years, 22.3% within 5–10 years, and 38.5% >10 years postpartum. 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 were observed in 10 studies comparing GL after pregnancy with nulliparous controls. Systematic review of the literature showed that mainly prepregnancy 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.

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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, a total of 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 wk of gestation), deliveries (45.6% versus 12.5%) and increased rates of small for gestational age and low birth weight (mean birth weight 2420 g versus 3298 g).[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

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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 preconceptional counseling of KT patients.

A meta-analysis of KT recipients published in 2011 analyzed graft loss (GL) incidence in a small number of retrospective studies, reporting 8% postpregnancy 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 serum creatinine (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 timings of pregnancy after KT are described as follows: an interval of >1 year between KT and pregnancy, and an interval of >1 year between the last episode of acute rejection. Furthermore, SCr levels should be below 1.5 mg/dL, no acute infections should be present, and stable maintenance of nonteratogenic 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 nonpregnant KT recipients and for the first time long-term (up to 10 y) 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.

MATERIALS AND METHODS

Search Strategy and Study Selection

A systematic search of literature was performed in Pubmed, Embase, and Cochrane library to identify all studies on SCr and GL after pregnancy in KT recipients until September 2018 (**Appendix 1, SDC**, http://links.lww.com/TP/B836). Two reviewers (A.S. and N.P.) 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 that reported <6 months postpregnancy follow-up were excluded.

Data Extraction

Two independent reviewers (A.S. and M.B.) extracted data from all eligible studies. The following data were extracted from each study: study outcomes on prepregnancy SCr, postpregnancy SCr, and GL or graft survival. For all the included studies, data on pre- and postpregnancy SCr were 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 11 studies, there were missing or incomplete data, this was requested from the authors and in 3 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 (eg, hypertension, proteinuria, SCr before pregnancy, and transplant to conception interval).

Pooled Estimates

To pool data on GL and postpregnancy SCr, subcategories were created based on the number of years postpartum. Articles on GL were divided into 4 categories based on timing since pregnancy: GL within 2 year postpregnancy, 2–5 year, 5–10 year postpregnancy, and >10 year postpregnancy. Data on SCr postpregnancy were divided into 3 subcategories: within 2 year postpregnancy, 2–5 years, and 5–10 years postpregnancy. The difference between postpregnancy SCr and prepregnancy 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 postpregnancy 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 (A.S. and M.B.) screened the studies for full text and performed a critical appraisal on applicability and validity (**Appendix 2, SDC**, http://links.lww.com/TP/B836). 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 3 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 postpregnancy (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 subanalysis 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.

Pooled Incidence of GL After Pregnancy in KT Recipients

A total of 38 studies reported on GL in 2453 recipients. Median follow-up time was very heterogenic among the studies and varied from 6 months until 15 years after pregnancy GL occurred in 321 (13%) patients following

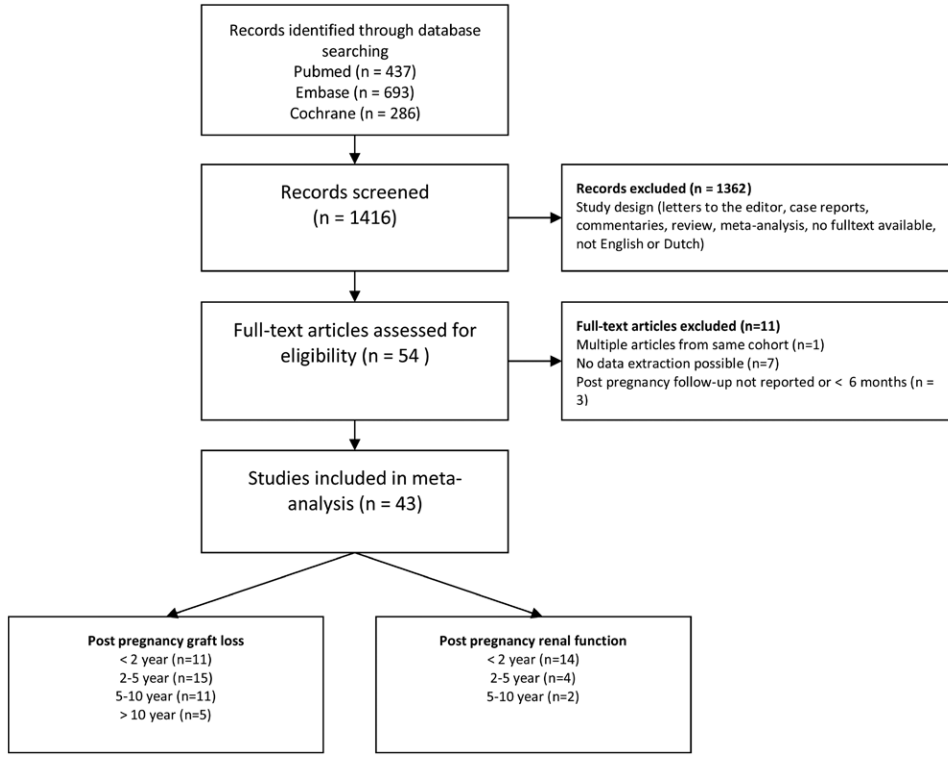

FIGURE 1. Study selection for studies reporting postpregnancy graft function and/or postpregnancy graft loss.

pregnancy. The risk on GL is increasing in time with pooled incidences of 9.4%, 9.2%, 22.3%, and 38.5% for <2 year, 2–5 year, 5–10 year, and >10 years after pregnancy, respectively (Figure 2A–D).

Among the 10 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) after pregnancy.

Pooled Incidence of SCr After Pregnancy in KT Recipients

The postpregnancy data of 18 individual studies on SCr within women were pooled in 3 postpartum time intervals. Fourteen studies reported on 1-year postpregnancy 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 prepregnancy SCr within 2-year postpregnancy SCr. (Figure 3A) Four studies reported on SCr 2–5 years following pregnancy, and only 2 studies on long-term (5–10 y) postpregnancy SCr and no significant differences were found when comparing pre- versus postpregnancy SCr (Figure 3B and C).

Predictors of Adverse Outcomes on Graft Function and Risk of GL

Among the included studies,[3,4,16,18,19,22,24,26,31,37,41-43,47,48,50,54] different predictors of adverse outcomes on graft function were described, including hypertension before pregnancy, presence of proteinuria before pregnancy, preeclampsia, SCr before 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.[23] 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 preeclampsia.[25] The type of immunosuppressive regime had no effect on graft survival.[38,48]

Preconceptional Hypertension as a Risk Factor for Accelerated GL

Four studies reported an effect of hypertension, before, or at the beginning of pregnancy, in relation to long-term graft function.[4,23,42,48] Hypertension was defined as blood-pressure >140/90 mm Hg. These 4 authors concluded that (drug treated) hypertension before 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, postpregnancy graft function (SCr) was compared between patients with hypertension before pregnancy (n = 5) and no hypertension before pregnancy (n = 15). The SCr was significantly worse ($P = 0.03$) in patients with hypertension before pregnancy.[23] Another study showed that hypertensive patients (n = 28) compared to normotensive patients (n = 23) had worse graft function (SCr) before pregnancy (1.39 mg/dL versus 1.10 mg/dL), $P \leq 0.01$.[47] Two recent studies of which one was a matched cohort study did not see a relation between graft failure and chronic hypertension.[22]

Preconceptional Proteinuria and Preconceptional SCr as Risk Factors for Accelerated GL

Proteinuria before or during pregnancy, especially proteinuria of >1 g/day, is associated with worse graft survival.[48,55] Two studies, which compared high levels of

TABLE 1.

Study characteristics and outcomes

Study y (country)	KT recipients (n)	Pregnancies[a] (n)	Mean age at conception (y)	Prepregnancy SCr, mg/dL	Post pregnancy SCr, mg/dL	Graft loss, %	Post pregnancy follow up (in mo)[b]	TCI (in mo)
Abe (2008)[23] 1977–2002 Japan	20	21	32.1 (range 25–40) at delivery	1.15 ± 0.27	1.29 ± 0.51	1 yr: 0% 5-10 yr: 20%	95	66 (range 24–135)[c]
Aivazoglou (2010)[24] 2006–2010 Brazil	31	34	26.5 (range 17–43)	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
Ajaimy et al (2016)[25] 2009–2014 USA	11	11	36 (range 22–38)	NR	NR	27.3%	27.3 (range 14.4–48)	42.4
Alfi (2008)[26] 1989–2005 Saudi-Arabia	12	20	30.5 ± 4.5	1.24 ± 0.27	1.76 ± 2.15	16.7%	NR	21 ± 5.7
Amine (2017)[27] 1992–2011 Tunisia	12	17	34.2	NR	NR	10%	72	46.9
Areia (2009)[28] 1989–2007 Portugal	28	34	27 ± 5.1	1.29 ± 0.34	1.34 ± 0.95	NR	12	51.3 ± 34.2 (3–134)
Basaran (2004)[29] 1975–2003 Turkey	8	8	29.3 ± 4.7	1.15 ± 0.2	1.42 ± 0.8	25%	67.2 ± 28.8[d]	43.2 (range 22.8–51.6)
Candido (2016)[30] 2004–2014 Portugal	36	41	28 ± 5	1.19 ± 0.07	1.59 ± 0.20	0.4%	SCr 12	51.3 ± 36
Crowe (1999)[31] 1972–1998 UK	29	33	29 (range 19–39)	1.77 ± 1.18	1.91 ± 1.18	10.3%	SCr 12	43 ± 6.9[e] (5–121)
Debska-Slizien (2014)[32] 1980–2012 Poland	17	19	30 ± 5	NR	NR	23.5%	102 (range 12–300)	40.8 ± 30
Di Loreto (2010)[33] 1997–2010 Italy	12	13	33.9 ± 3.1	NR	NR	0%	24	53.4 ± 37.8[c]
El Houssni (2016)[34] 1998–2012 Morocco	12	18	29.9 ± 5.3	NR	NR	0%	112 (27.25)[f]	42 (47.5)[f]
Farr (2014)[35] 1999–2013 Austria	10	12	34 ± 4	NR	NR	0%	128 ± 50[d]	79 ± 36[c]
First (1995)[15] 1967–1990 USA	18	22	NR	NR	NR	16.7%	82.8 (range 43.2–164.4)	59 (range 2–221)
Fischer (2005)[16] NR Germany	81	81	29 ± 0.5 at delivery	NR	NR	8.6%	91.3 ± 5	41.8 ± 3.2
Galdo (2005)[36] 1982–2002 Chile	30	29	NR	1.19 ± 0.38	1.38 ± 0.53	NR	12	46.6 ± 35.5 (6–108)
Gaughan (1996)[37] 1991–1996 USA	15	13	29.5 ± 5.2	NR	NR	6.7%	24	70.8 ± 10.8
Ghafari (2008)[38] 1991–2007 Iran	53	61	24.5 (range 19–38)	NR	NR	5.7%	32 (range 12–120)	32.4 (range 20.4–63.6)
Gorgulu (2010)[39] 1983–2008 Turkey	19	19	29 ± 3	1.06 ± 0.3	1.15 ± 0.29	NR	96 ± 36	60 ± 36
Hebral (2014)[40] 1969–2011 France	46	61	31 (24–43)	NR	NR	1 y: 6.5% 5–10 y: 18.3%	72	60 (222)[f]

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TABLE 1. (Continued)

Study y (country)	KT recipients (n)	Pregnancies[a] (n)	Mean age at conception (y)	Prepregnancy SCr, mg/dL	Post pregnancy SCr, mg/dL	Graft loss, %	Post pregnancy follow up (in mo)[b]	TCI (in mo)
Hooi et al (2003)[41] 1975–2001 Malaysia	46	51	30.7 ± 4.7	1.27 ± 0.37	1.35 ± 0.44	8.7%	58.8 ± 42	54 ± 37.2
Kashanizadeh (2007)[17] 1996–2002 Iran	86	62	NR		NR	9.3%	45 ± 22	31 ± 15 (12–85)
Kato (2012)[42] 1973–2009 Japan	23	22	31.3 ± 3.6 at delivery	1.16 ± 0.39	1.4 ± 0.8	8.7%	SCr 12	70.8 ± 38.2
Keitel (2004)[43] 1977–2001 Brazil	41	28	NR	1.2 ± 0.5	2.0 ± 1.8	<2 y: 14.6% >10 yr: 43.9%	GL 24 SCr 6	NR
Kim (2008)[18] 1991–2005 Korea	48	52	31.6 ± 4.1	1.12 ± 0.25	1.1 ± 0.98	18.8%	114 (range 44.4–184.8)[d]	40.2 ± 27.1
Kwek (2015)[44] 2001–2012 Singapore	9	10	34.6 (range 32.8–36.8) at delivery	1.39 ± 0.25	2.23 ± 1.26	11.1%	GL 37 SCr 12	69 (38–97)[f]
Levidiotis (2009)[14] 1966–2006 Australia	118	118	NR for this sub analysis	NR	NR	15 y: 43.5	67.2	NR
Little (2000)[45] 1985–1998 Ireland	19	25	30.3 (range 19.9–42.8)	1.59 ± 0.46	1.71 ± 0.68	15.8%	33.2 (range 1–115)	48 (range 2.4–102)
Melchor (2002)[46] 1973–1998 Mexico	21	26	30.8 ± 7.1		NR	4.8%	24	49
Moritz (2018)[2] 1967–2017 USA	1100	1980	NR	NR	NR	<2 y: 10.1%	188.4 ± 132	5.4 ± 4.3
O'Reilly (2001)[47] 1967–1998 UK	41	57	29.7 (range 18–37)	NR	NR	9.8%	60	92.4 (12–288)
Pour-Reza-Gholi (2005)[19] 1984–2004 Iran	60	41	29.8 ± 4.7	NR	NR	39.1%	100.8 ± 48.5	27.5 (range 1–114)[f]
Queipo-Zaragoza (2003)[48] 1980–2000 Spain	29	32	29.6 ± 4.8	NR	NR	17.2%	60	45.6 ± 40.7
Rahamimov (2006)[20] 1983–1998 Israel	39	55	NR	NR	NR	5–10 y: 23.1% >10 y: 35.9%	168 (range 72–264)[d]	42 ± 27.1
Salmela (1993)[49] 1964–1989 Finland	22	22	NR	NR	NR	36.4%	90	57.6[c]
Sibanda (2007)[4] 1994–2001 UK	176	157	30 (range 20–43) at delivery	NR	NR	5.8%	24	72 (range 3–228)
Stoumpos (2016)[3] 1973–2013 UK	89	104	30.3 ± 5.1	1.45 ± 0.87	1 y: 1.62 ± 1.21 5 y: 1.86 ± 1.6 10 y:1.51 ± 0.56	15.7%	98.4 (157.2)[f]	NR
Sturgiss (1995)[21] 1967–1987 UK	18	18	NR	1.06 ± 0.29	1.26 ± 0.83	>10 y: 5.6%	144 (range 48–276)	132 ± 60
Svetitsky (2018)[22] 2001–2017 Israël	18	22	29.6 (range 2339.2) at delivery	1.17 (range 0.7–3.1)	NR	NR	148.8 ± 57.4	75.7 (range 34–147.8)
Thompson (2003)[50] 1976–2001 UK	24	42	30 (range 19–39)	1.18 ± 0.43	1.24 ± 0.69	16.7%	46 (range 12–151.2)	54 ± 37.2

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TABLE 1. (Continued)

Study y (country)	KT recipients (n)	Pregnancies[a] (n)	Mean age at conception (y)	Prepregnancy SCr, mg/dL	Post pregnancy SCr, mg/dL	Graft loss, %	Post pregnancy follow up (in mo)[b]	TCI (in mo)
Vannevel (2018)[51] 1988–2015 Belgium, Canada Switzerland, Canada, Ireland, and Austria	52	52	32.8 ± 4.5	NR	NR	33%	69.6 (range 15.6–330)	74 ± 45
Yassaee (2007)[52] 1996–2001 Iran	74	74	29.3 ± 6.7	NR	NR	4.1%	2	41 ± 9.5
Yildirim (2005)[53] 1998–2005 Turkey	17	16	27.6 ± 5.8	1.18 ± 0.16	1.19 ± 0.12	0%	6	31.2 (range 3–98)

Serum creatinine (SCr) in mg/dL (in mean ± SD or median [range]).
[a]Only pregnancies >24 wk, follow up in months.
[b]In case of no mean follow up post pregnancy was reported, an explanation of outcomes is reported.
[c]TDI: transplant to delivery interval in months.
[d]Posttransplantation follow up, TCI: transplant to conception interval in months (mean ± SD, or mean [range]).
[e]SEM.
[f]Median (IQR).
GL, graft loss; IQR, interquartile range; KT, kidney transplantation; NR, not reported; SEM, standard error of the mean.

proteinuria (>0.3 or 0.5 g/d), found no deleterious effect on SCr or GL.[50,54]

Ten different studies analyzed the influence of prepregnancy SCr on graft outcomes (SCr postpregnancy 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.[18,24,26,42,43,47,48,50,54] Ten studies found a negative effect on graft function in patients with high SCr before pregnancy. Eight of them used SCr > 1.47 mg/dL as cut off point,[18,24,26,31,43,47,48,50] 1 study defined worse graft function as >1.24 mg/dL, 2 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 prepregnancy SCr and GL (OR –0.11, 95% CI [–0.44 to 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 postpregnancy graft function in women with high SCr before pregnancy[41,54] (Table 3).

Pre-eclampsia as a Risk Factor for Accelerated GL

The development of pre-eclampsia during pregnancy was mentioned by 1 study as factor for graft dysfunction during pregnancy.[24] Pre-eclampsia was defined as hypertension and proteinuria >0.30 g/24 h. One study showed that pre-eclampsia was a "borderline" risk factor for GL (OR 1.09; 95% CI [0.92-1.34], $P = 0.09$).[22] The latest matched cohort study did not see a relation between pre-eclampsia and GL.[51]

Transplant to Conception Interval as a Risk Factor for Accelerated GL

The relationship between transplant to conception interval (TCI) and graft function is reported by 5 individual studies, which report on different outcomes of TCI (in general, TCI < 1 y, TCI < 2 y, TCI > 5 y).[3,16,19,26,37] Stoumpos et al found no negative relationship between graft function and TCI.[3] One study found more GL in patients with TCI < 1 year,[26] 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 < 2 year, compared to other subgroups.[16] A TCI of >5 years has acceptable outcomes on postpregnancy graft function and rejection during pregnancy and up to 3 months postpartum.[37]

Assessment of Quality and Publication Bias

We assessed study quality with the use of critical appraisal on applicability and validity (**Appendix 2, SDC**, http://links.lww.com/TP/B836). Seventeen studies had a sample size of <20 women. Missing data were not well described in 21 of the studies. Ten studies did not describe their statistical analysis precisely. In 6 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, SDC**, http://links.lww.com/TP/B836). There is a funnel-plot asymmetry in the subgroup of Δ SCr <2 years after pregnancy indicating publication bias toward the publication of small studies with positive Δ SCr values (**Appendix 4A, SDC**, http://links.lww.com/TP/B836).

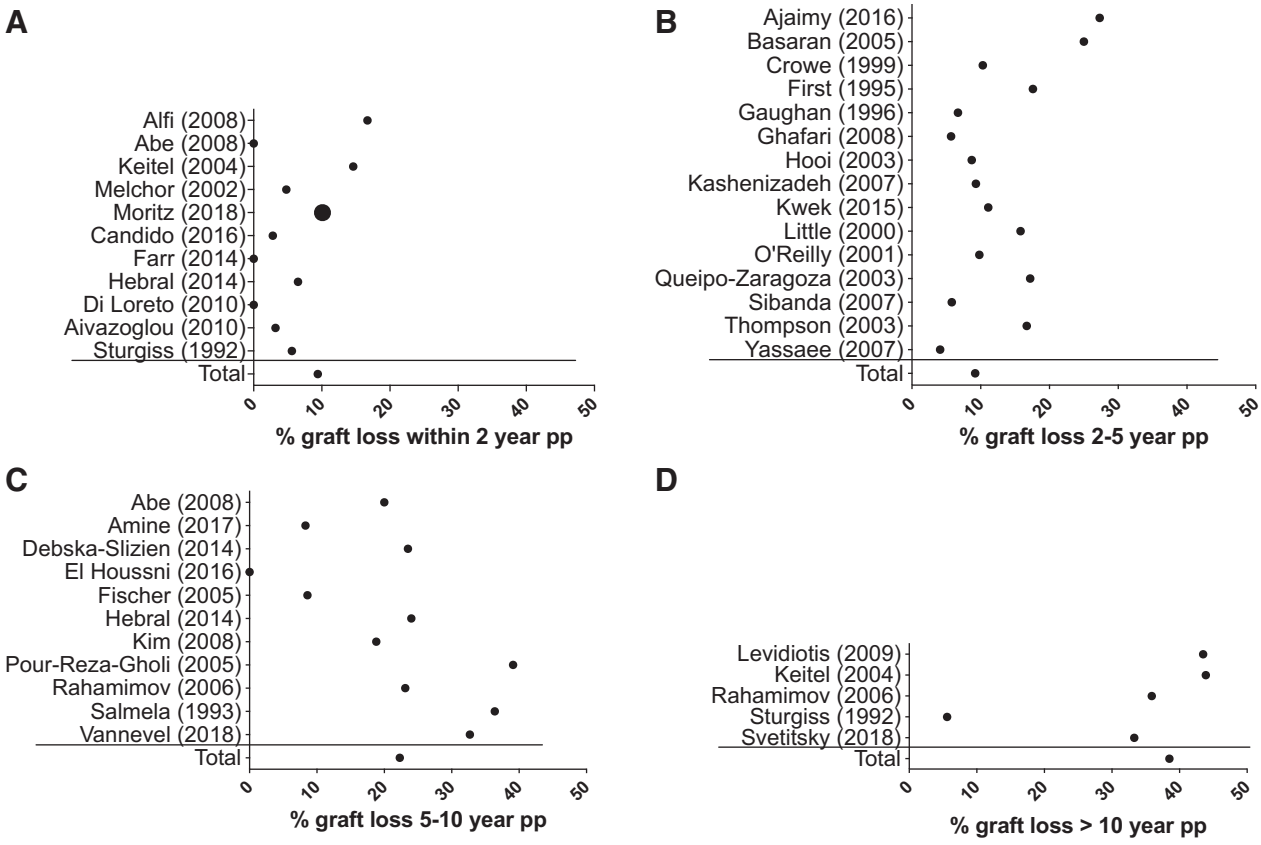

FIGURE 2. A–D, Pooled incidence of postpregnancy graft loss. A, Graft loss within 2 y postpregnancy: 9.4%, n = 1347 (range 10–1100), total graft loss n = 126 (range 0–111). B, Graft loss 2–5 y postpregnancy: 9.2%, n = 600 (range 8–139), total graft loss n = 55 (range 1–8). C, Graft loss 5–10 y postpregnancy: 22.3%, n = 395 (range 12–81), total graft loss n = 88 (range 0–18). D, Graft loss >10 y postpregnancy: 38.5%, 234 (range 18–118), total graft loss n = 90 (range 1–51).

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 preconceptional 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 2 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 >500 women from 23 additional studies to the literature since the last meta-analysis from 2011 on the subject.[1] We report slightly higher outcomes on GL within 2 years (9.4% versus 8%) and higher numbers of GL of 22.3% versus 19% after 5–10 years postpregnancy, this was mainly caused by the TPR report.[2] Desphande reported 12.5-year postpregnancy 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% >10-year postpartum is based on a pooled incidence of 5 new studies.[14,20-22,43]

We added 10 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 posttransplant. Unfortunately, posttransplant 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 postmortal donors) is 46% and 15 years GL is 60% for this age group in the Eurotransplant region.[56] 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

TABLE 2.

Characteristics matched cohort studies on graft loss

	N					Graft loss, %			
	Index	Control	Reference point	Matched for	Median FU time after pregnancy, mo	Index	Control	Odds ratio	*P*
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)[a]	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

[a]IQR.

ESRD, end-stage-renal-disease; FU, follow-up; HLA MM, human leucocyte antigen mismatch; IS medicine, immunosuppressive medicine; IQR, interquartile range; KT, kidney transplantation; N, number of participants; NR, not reported; PRA, panel reactive antibody; TCI, transplant to conception interval; TDI, transplant to delivery interval.

1. Age at KT; 2. Y 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.

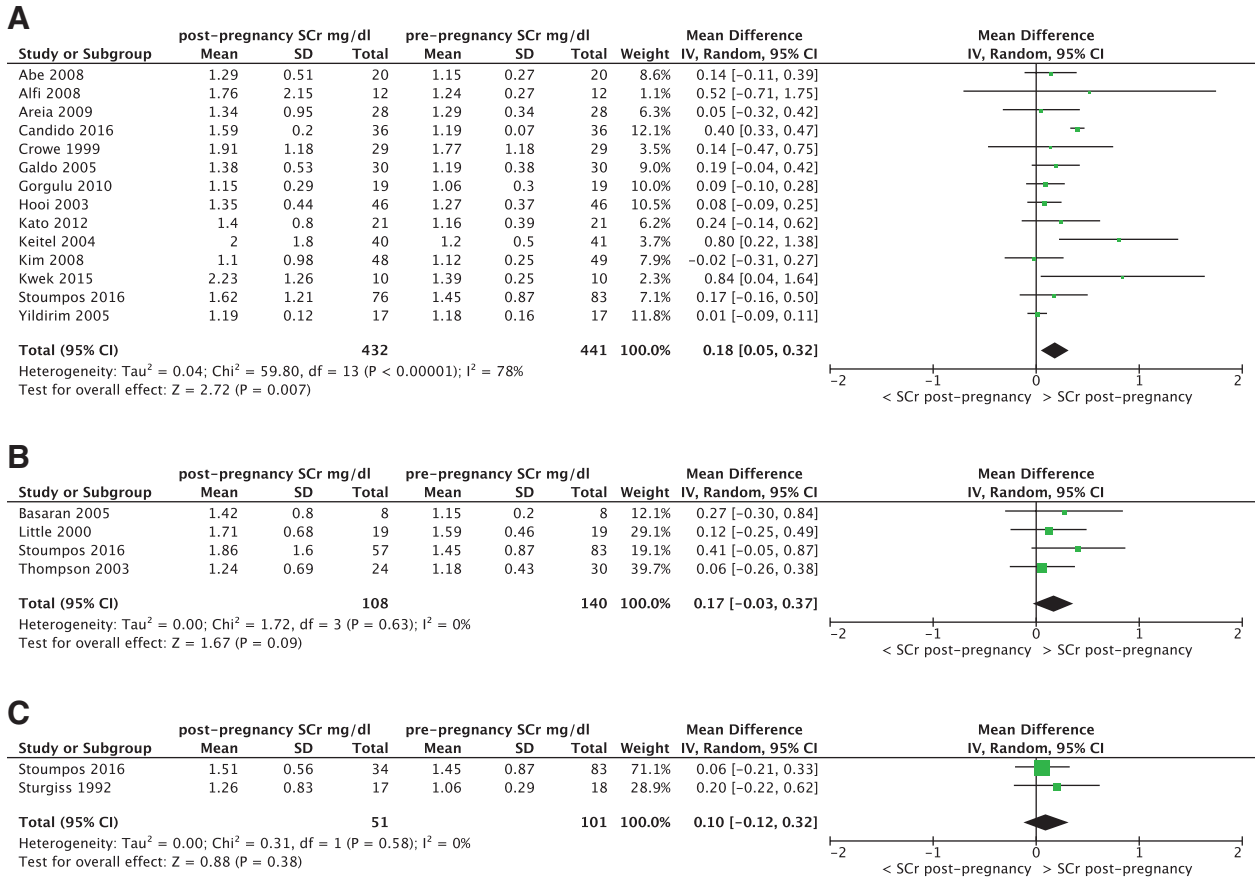

FIGURE 3. A–C, Pooled difference (mean difference [95% CI] in prepregnancy SCr and postpregnancy SCR (Δ SCr pre- and postpregnancy). A, Delta SCr within 2 y postpregnancy: SCr 0.18 mg/dL [0.05, 0.32], $P = 0.007$, n = 441. B, Δ SCr 2–5 y postpregnancy: SCr 0.17 mg/dL [–0.03, 0.37], $P = 0.09$, n = 175. C, Δ SCr 5–10 y postpregnancy: SCr 0.10 mg/dL [–0.12, 0.32], $P = 0.38$, n = 101. CI, confidence interval; SCr, serum creatinine; SD, standard deviation.

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 2 years after delivery as described in 87 KT recipients derived from 3 studies.[30,43,44] Possibly, this might be caused by physiological changes after pregnancy or restart of medication such as ACE inhibitors. On the contrary, this could be the result of high rate of risk factors in the study population (65.9% hypertension, 36.5% SCr >1.5 mg/dL before pregnancy[43]), 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.[57]

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.[9,10] The TCI is a point of discussion as it was stated by the European guidelines for 2 years after KT. The American guidelines changed their advice to postpone pregnancy at least until 1 year after pregnancy. Studies such as Fischer and Pour Reza Gholi showed reassuring results of pregnancies after 1 year after pregnancy.[16,19] Pregnancy within 1 year after KT is associated with an increased risk on GL, which Rose et al showed in their recent study.[58] Data on the association of pre-eclampsia with GL show confliction results.[23,24,51]

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 after 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, SDC**, http://links.lww.com/TP/B836). In addition, this is an unadjusted meta-analysis in which we could not account for factors such as differences in healthcare 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 estimated glomerular filtration rate (eGFR). Most studies only report SCr without age, calculation of eGFR was not possible.[59] We assumed that preconceptional creatinine was really preconceptional as it was

TABLE 3.

Predictors of graft loss or renal function deterioration after pregnancy

	Negative association		No association	
Risk factors	**Unit**	**Author**	**Unit**	**Author**
Hypertension	>140/90 mm Hg	Queipo Zaragoza (2003)	Pre-existing hypertension	Stoumpos (2016)
Before or at the beginning of pregnancy	Drug-treated hypertension	Sibanda (2007), Abe (2008), Kato (2012)	Chronic hypertension Chronic hypertension	Svetitsky (2018) Vannevel (2018)
Proteinuria	>1 g/d	Queipo Zaragoza (2003)	>0.3 g/d >0.5 g/d	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)
Prepregnancy 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 –011; 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 y	Alfi et al (2008)	General <1 y <2 y >5 y Mo (OR, 0.05; 95% CI [-0.07 to 0.18], $P = 0.42$)	Stoumpos (2016) Fischer (2005) Pour-Reza-Gholi (2005) Gaughan (1996) Vannevel (2018)

CI, confidence interval; SCr, serum creatinine.

stated in the text. It could be possible that the preconceptional SCr that was used for the included studies were not completely preconceptional and that the SCr was already physiologically increased. Ultimately, evaluation of individual slope of eGFR pre- and postpregnancy would be performed by means of a multilevel 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 postpartum, but no association at longer periods of time after delivery. The incidence of GL up to 10 years postpregnancy 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 preconceptional counseling. Based on the risk factors for GL, it could be concluded that if prepregnancy KT function is good, it remains good after pregnancy. Systematic review of the literature showed that mainly prepregnancy proteinuria, hypertension, and high SCr are risk factors for GL.

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