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

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Although numbers of pregnancy after kidney transplantation (KT) are rising, high risks of adverse pregnancy outcomes (APO) remain. Though important for pre-conception counselling 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 of 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 birth weight under 2500 gram, preterm birth under 37 weeks, third trimester severe hypertension (systolic blood pressure over 160 and/or diastolic blood pressure over 110 mm Hg) 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 birth weight 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 counselling 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.

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The first successful pregnancy after kidney transplantation (KT) was reported in 1958.[1] Today, approximately 6 of 100,000 births in the United States result from pregnancies in women with a KT, corresponding to 227 births annually.[2,3] Although the annual numbers of pregnancy after KT are rising, challenges remain prominent. High incidences of adverse pregnancy outcomes such as pre-eclampsia (PE), hypertensive disorders of pregnancy, fetal growth restriction, and preterm birth have been reported.[4-6] Although previous studies on pregnancy outcomes in women with chronic kidney disease (CKD) and after KT have been conducted,[7-10] data on pregnancy outcomes after KT analyzed per consecutive prepregnancy estimated glomerular filtration rate (eGFR)-CKD category (including advanced stages)[11] on a large scale are still missing. This is essential information for pre-pregnancy 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 analyze the risks of adverse pregnancy outcomes after KT—depending on the prepregnancy eGFR-CKD category—and to identify risk factors for adverse outcomes in a large nationwide cohort.

METHODS

Study design and participants

We performed a retrospective cohort study using patient data originating from the PARTOUT (Pregnancy After Renal Transplantation OUTcomes) network. The PARTOUT network was established in

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2017 by a collaboration between obstetricians and transplant nephrologists in all 8 kidney transplant centers in the Netherlands. Consecutive pregnant kidney transplant recipients (KTRs) transplanted between 1971 and 2017 were identified via a systematic search in the National Organ Transplant Registry. In this registry, all transplanted patients in the Netherlands are registered. With a lack of information on pregnancy after KT, the National Organ Transplant Registry was only used for patient identification and not for data collection. The patient search was completed with questioning transplant nephrologists and gynecologists in participating centers. Of note, KT and care for pregnancies after KT are centered in university medical centers 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 KTRs. Twin pregnancies were excluded because of a higher incidence of maternal and neonatal complications.[13,14] Data were collected until December 31, 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 were registered using standardized case record forms (OpenClinica open source software, version 3.1).[15] Baseline characteristics including information on underlying kidney disease, KT, obstetric history, transplant-conception interval, and use of medication were collected. Prepregnancy eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration 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 birth weight below the fifth or tenth 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.

Serum creatinine (SCr) values were documented both prepregnancy, by selecting the closest outpatient clinic value before conception, and during each trimester of pregnancy. When multiple values in 1 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 gynecologists to ensure representivity.

Data on antihypertensive and immune suppressive medication were 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 guideline as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg 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 lack of a proper definition for PE in women with CKD, (superimposed) PE in obstetric history or during pregnancy was defined by the attending physician at the 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 systolic blood pressure and diastolic blood pressure values. Midterm blood pressure drop was defined as the absolute difference between MAP during the second trimester of pregnancy and prepregnancy MAP.[24-27] Midterm glomerular hyperfiltration was assessed by studying the absolute (in μmol/l) and percentage (%) dip in SCr between 8 and 20 weeks of gestation compared with prepregnancy SCr.[28,29]

Study endpoints

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

Patients were lost to follow-up on the composite endpoint when (i) data were missing on all 4 components or (ii) ≥1 of the individual components were missing and other components of the composite endpoint were scored negative. These pregnancies could not be analyzed in prediction analysis.

Patients were included over a long time in which policy changes occurred, such as the wide introduction of calcineurin inhibitors (CNIs) in the 1990s, prescription of acetylsalicylic acid for PE 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 CNIs (cyclosporine and tacrolimus). Furthermore, transplant era ("before the introduction of cyclosporine" [<1990] and "after the introduction of cyclosporine and tacrolimus" [>1990]) and decennium were assessed in prediction analysis.

The PARTOUT network investigated pregnancy outcomes stratified per use of CNIs earlier.[37] Therefore, we provide only 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

Because 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% confidence interval [CI]). To allow for the nonindependence of multiple pregnancies in 1 woman, the data had a multilevel structure and were analyzed using a generalized estimating equation. This is an established method for multilevel analysis.

Pregnancy outcomes per prepregnancy eGFR-CKD category were analyzed for the total cohort. Variables associated with the cAPO

were initially identified by univariable generalized estimating equation analysis, followed by multilevel generalized estimating equation analysis to assess independency of the associations. Of note, the association between possible predictors and the cAPO was analyzed without building a prediction model. Odds ratios with corresponding 95% CIs were calculated. Univariable generalized estimating equation analyses were performed using an unstructured correlation matrix structure. For multivariable analyses, an exchangeable correlation matrix structure was used. Before prediction analyses, missing predictor values were imputed to avoid only including the complete cases for analysis.[38]

Multiple imputation was performed with 20 imputation rounds. Distribution of predictors before and after imputation was investigated to check for imbalances. Candidate predictors for the adverse pregnancy outcome were selected based on previous literature and included maternal age, body mass index, transplantation-conception interval, decennium, transplant era, prepregnancy eGFR, obstetric history (i.e., preterm birth, PE), 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 was assessed, comparing complicated pregnancies with uncomplicated pregnancies.

Lastly, the risk of graft loss after pregnancies with the cAPO 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 a functioning graft until December 31, 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 cAPO 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 the exclusion of 13 twin pregnancies, 288 singleton pregnancies were included for analysis. Baseline characteristics and pregnancy outcomes of twin pregnancies are shown in Supplementary Tables S1 and S2, respectively. 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 1980s to 47.53 in the last decennium.

Neonatal outcomes

The study outcomes for the total cohort are shown in Table 2. The total live birth rate ≥20 weeks of gestation was 93%. Neonatal death occurred in 8 of 255 (3%) pregnancies, of which 5 (63%) occurred before the year 2000 and 3 (38%) in the period after 2000. Preterm birth occurred in 50% of pregnancies. The mean gestational age was 249 days (SD: 30) 35.6 weeks. For preterm births, the mean duration of pregnancy was 230 days (SD: 29), 32.9 weeks. The mean birth weight was 2383 (SD: 885) g, corresponding to a median percentile corrected for gestational age of 13 (IQR: 46). Birth weight <2500 g was seen in 49% of pregnancies. A total of 15 of 180 (8%) babies had Apgar scores of ≤5 five minutes after delivery, and 28 of 202 (14%) were admitted to a neonatal intensive care unit. For these parameters, a large amount of missing values existed (35% for Apgar scores and 30% for neonatal intensive care unit 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) PE. Overall, mean systolic blood pressure increased over time from 122 (SD: 10.5) mm Hg in the first trimester to 123 (SD: 11.6) mm Hg in the second and 129 (SD: 12.9) mm Hg in the third trimester. In 163 of 231 (71%) (missing data 20%) pregnancies, antihypertensive medication was used. A summary of antihypertensive and immune suppressive medication during pregnancy is shown in Supplementary Tables S3 and S4, respectively. During pregnancy, the use of antihypertensive medication increased. Of all pregnancies with antihypertensive medication use, 132 of 163 (59%) used medication during the first trimester, 138 of 163 (85%) during the second, and 151 of 153 (99%) during the third. The use of triple medication increased from 3% during the first trimester, to 6% during the second and 13% during the third. Almost all pregnancies with triple medication in the third trimester scored positive on our cAPO (19 of 20). The mean prepregnancy eGFR was 61 (SD: 21) ml/min per 1.73 m^2. The median time between prepregnancy SCr measurement and conception was 37 (IQR: 56) days. The mean SCr was 108 (SD: 51.4) μmol/l during the first trimester, 108 (SD: 58.1) μmol/l during the second, and 120 (SD: 53.7) μmol/l during the third trimester.

Cesarean section occurred in 48% of pregnancies. Of preterm births, 41% were vaginal deliveries, of which 58% were induced, as well as 10% of cesarean sections. Iatrogenic preterm birth increased over time (Supplementary Tables S5 and S6) and occurred in 79% of preterm pregnancies.

Transplant eras and decades

Baseline characteristics and pregnancy outcomes stratified per decennium and per use of CNIs are shown in Supplementary Tables 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 CNIs increased. In pregnancies within the transplant era "after cyclosporine and tacrolimus" and with the use of CNIs, more gestational hypertension occurred (61% vs. 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.

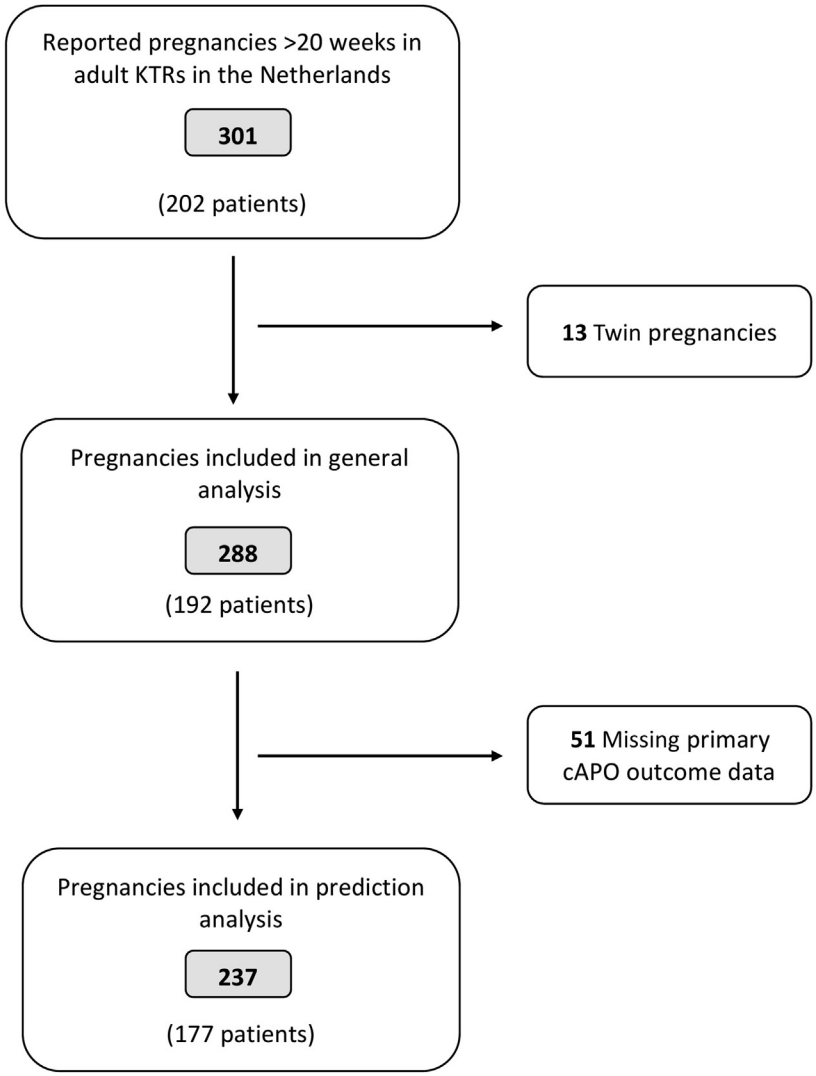

Figure 1 | Flowchart of this study. Consecutive pregnancies in kidney transplant recipients (KTRs) between 1971 and 2017 were identified via the National Organ Transplant Registry and via transplant nephrologists in all university medical centers in the Netherlands, ensuring nationwide consecutive inclusion. 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 combined adverse pregnancy outcome (cAPO) data were excluded.

Predictors of the combined adverse pregnancy outcome

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

In pregnancies with complete follow-up, the cAPO was observed in 186 of 237 (78%) pregnancies (Supplementary Table S9). Baseline characteristics of pregnancies included in prediction analysis are shown in Supplementary Table S10. Pregnancies with missing data on the composite endpoint are reported in Supplementary Table S11. As shown in Supplementary Table S10, pregnancies with the cAPO had a lower prepregnancy eGFR. As shown in Supplementary 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 to the observed data (Supplementary Table S12 and Figure S1)

When comparing cAPO to no-cAPO pregnancies, the mean midterm MAP drop was significantly smaller in pregnancies with the cAPO, mean difference −6.1 (SD: 24.6), *P* value of 0.001 (Figure 2). Also, the midterm percentage SCr dip was significantly smaller in pregnancies with the cAPO, mean difference −4.5%, *P* value of 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 cAPO with the odds ratio of 0.98 (95% CI: 0.96–9.99). During pregnancy, midterm MAP dip and midterm percentage SCr dip were independent predictors for the cAPO with the corresponding odds ratios of 0.94 (95% CI: 0.90–0.98) and 0.95 (95% CI:

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

Variable	All pregnancies ($N = 288$)	eGFR ≥90 ml/min per 1.73 m^2 ($N = 23$)	eGFR 90–60 ml/min per 1.73 m^2 ($N = 104$)	eGFR 59–45 ml/min per 1.73 m^2 ($N = 72$)	eGFR 44–30 ml/min per 1.73 m^2 ($N = 44$)	eGFR <30 ml/min per 1.73 m^2 ($N = 10$)
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
Autoimmune	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) pre-eclampsia 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, yr (IQR)	5 (7)	5 (9)	6 (7)	4 (5)	6 (6)	5 (4)
Caucasian ethnicity	174/207 (84)	11/15 (73)	66/78 (85)	40/48 (83)	37/40 (93)	6/8 (75)
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)

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KT, kidney transplantation; TCI, transplant-conception interval.

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: $n = 265$; birth weight: $n = 261$. eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration method, categories corresponding to CKD stages.

0.93–0.98). Decade of pregnancy and "transplant era" had no significant association with the cAPO.

Risk of graft loss after pregnancy

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

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 3 major findings. First, overall obstetric outcomes in KTRs are positive with 93% live birth rate >20 weeks of gestation, mean gestational age 35.6 weeks, and mean birth weight 2383 (SD: 885) g. Second, this study shows that pregnancy outcomes in women with poor prepregnancy kidney function are also relatively good. Also, prepregnancy eGFR, midterm percentage SCr dip, and midterm 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 not a 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, for example, additional ultrasounds can be organized and/or medication can be adjusted and pregnancy might be prolonged.

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

Variable	All pregnancies ($N = 288$)	eGFR ≥90 ml/min per 1.73 m^2 ($N = 23$)	eGFR 89–60 ml/min per 1.73 m^2 ($N = 104$)	eGFR 59–45 ml/min per 1.73 m^2 ($N = 72$)	eGFR 44–30 ml/min per 1.73 m^2 ($N = 44$)	eGFR <30 ml/min per 1.73 m^2 ($N = 10$)
Neonatal outcomes						
Gestational age, d (SD)	249 (30)	264 (18)	253 (27)	244 (32)	241 (33)	221 (32)
Gestational age, wk	35.6	37.7	36.1	34.9	34.4	31.6
Preterm birth,[a] wk	132/265 (50%, 42%–59%)	7/22 (32%)	41/99 (41%)	42/71 (59%)	25/42 (60%)	9/10 (90%)
<34	64/265 (24%, 19%–31%)	2/22 (9%)	14/99 (14%)	23/71 (32%)	16/42 (38%)	6/10 (60%)
<28	18/265 (7%, 4%–11%)	0	5/99 (5%)	4/71 (6%)	6/42 (14%)	2/10 (20%)
Birth weight, g (SD)	2383 (885)	2846 (753)	2512 (724)	2388 (940)	2087 (937)	1335 (725)
<2500[a]	129/261 (49%, 43%–55%)	6/21 (29%)	42/96 (44%)	32/69 (46%)	28/41 (68%)	10/10 (100%)
<1500	41/261 (16%, 11%–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%–51%)	8/21 (38%)	33/90 (36%)	25/65 (39%)	21/40 (53%)	7/10 (70%)
<p5	64/243 (26%, 20%–34%)	4/21 (19%)	22/90 (40%)	18/65 (28%)	10/40 (25%)	5/10 (50%)
Apgar ≤5, 5 min 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%)
Stillbirth	19/282 (7%, 4%–10%)	0	4/103 (4%)	6/71 (8%)	4/44 (9%)	0
Neonatal mortality (in first 7 d of life)	8/255 (3%, 2%–6%)	1/23 (4%)	1/97 (1%)	2/64 (2%)	1/38 (3%)	2/9 (22%)
Maternal outcomes						
Gestational hypertension	61/233 (26%, 21%–32%)	6/17 (35%)	42/86 (49%)	39/63 (62%)	23/39 (59%)	4/6 (67%)
(Superimposed) pre-eclampsia	81/235 (34%, 29%–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%–3.9%)	0	2/83 (2%)	0	1/38 (3%)	0
Use of calcineurin 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%–91%)	13/21 (62%)	60/83 (72%)	50/64 (78%)	37/43 (86%)	10/10 (100%)

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NICU, neonatal intensive care unit.

[a]Variables that are part of the composite outcome.

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, and for continuous variables, the number of complete cases are described here: gestational age, $n = 265$. Percentile corrected for gestational age, $n = 243$. eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration method, categories corresponding to CKD stages.

Table 3 | Univariable and multivariable analysis of predictors of the composite adverse pregnancy outcome

Predictor	Odds ratio	95% CI
Univariable analysis		
Age at pregnancy, yr	1.020	0.961–1.083
BMI at pregnancy, kg/m^2	1.013	0.929–1.105
Transplant-conception interval, yr	1.020	0.950–1.096
Hypertension before pregnancy	1.100	0.547–2.212
eGFR prepregnancy,[a] ml/min per 1.73 m^2	0.980	0.966–0.994
Percentage SCr drop,[a] %	0.963	0.935–0.991
MAP before pregnancy, mm Hg	0.993	0.957–1.029
MAP drop second trimester,[a] mm Hg	0.942	0.908–0.977
Cadaver kidney transplant	0.965	0.500–1.860
Diagnosis kidney disease before KT		
Glomerulonephritis	1.255	0.499–3.158
Other	0.984	0.404–2.396
History of preterm birth	1.452	0.427–4.938
History of pre-eclampsia	1.134	0.248–5.186
Multipara	0.133	0.461–1.448
Decade of delivery		
1980–1990	2.522	0.674–9.431
1990–2000	1.192	0.494–2.881
2000–2010	0.670	0.324–1.386
2010–2017	Reference	Reference
Transplant era		
Before CyA (<1990)	2.484	0.736–8.373
After CyA and tacrolimus (>1990)	Reference	Reference
Multivariable analysis		
eGFR prepregnancy,[a] ml/min per 1.73 m^2	0.977	0.961–0.993
Percentage SCr drop,[a] %	0.953	0.925–0.981
MAP drop second trimester,[a] mm Hg	0.938	0.901–0.976

BMI, body mass index; CI, confidence interval; CyA, cyclosporine; eGFR, estimated glomerular filtration rate; KT, kidney transplantation; MAP, mean arterial pressure; SCr, serum creatinine.
Percentage SCr drop = percentual drop between the lowest SCr 8–20 weeks and prepregnancy SCr.
[a]Statistically significant, P value < 0.05.

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 of 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 KTRs and women with CKD, KTRs 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 impairment mechanisms and different therapies being used. Often no distinction is made in underlying kidney disease although this matters for the outcome.[52] Furthermore, the physiological SCr rise in the third trimester[53] might be understood as a process mimicking PE, in the absence of a proper definition for women with CKD. This could explain variation in the 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 with a recent study in CKD stages 3–5 including 43 KTRs without showing separate outcomes for KTRs.[7]

The association between midterm percentage SCr dip, midterm MAP dip, and the cAPO 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 after pregnancy with a median follow-up of 7 (IQR: 13) years 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.*[37] investigated the influence of CNIs on pregnancy outcomes and found no significant adverse outcomes. However, there is a time effect leading to bias because of the introduction of CNIs only in the 1990s 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 KTR population suggested that 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, lack of information on ultrasounds or dopplers makes the establishment of true fetal growth restriction 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 imputation for prediction analysis.[62-64] With limited bias, our results are generalizable for most settings.

This study has several limitations. First, because of 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

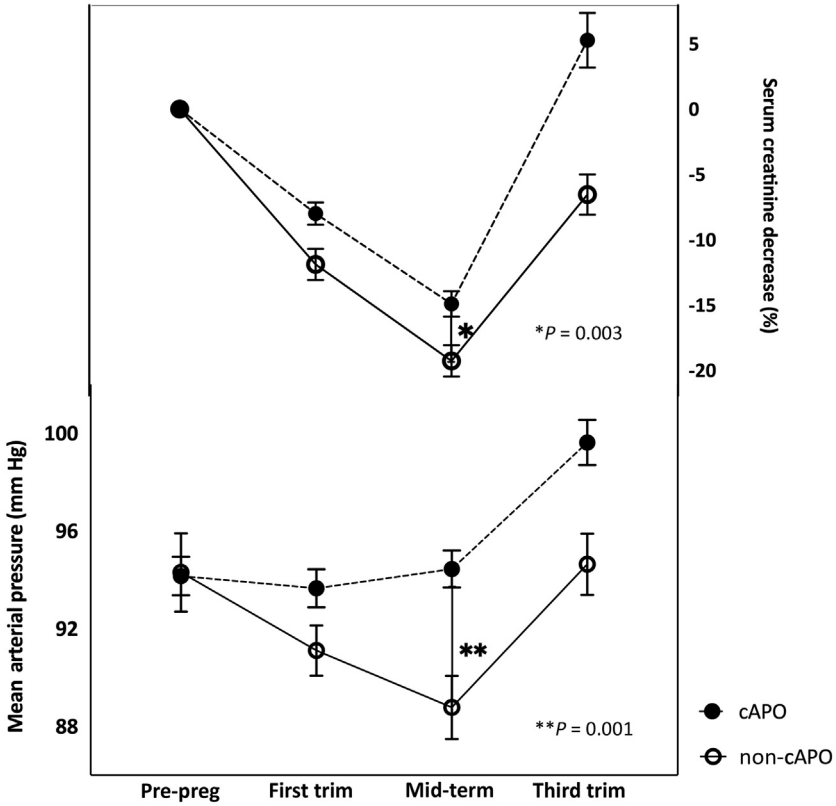

Figure 2 | Serum creatinine (Scr) and mean arterial pressure (MAP) during pregnancy after kidney transplantation: combined adverse pregnancy outcome (cAPO) pregnancies compared with non-cAPO. Data are presented as mean (SEM). *P* values are shown for the midterm delta MAP (absolute difference between second trimester and prepregnancy MAP) and serum creatinine decrease (% difference between SCr 8–20 weeks of gestation and prepregnancy SCr). Pre-preg, prepregnancy; First trim, first trimester; Mid-term, for MAP: second trimester, for SCr dip: 8–20 weeks of gestation; Third trim, third trimester.

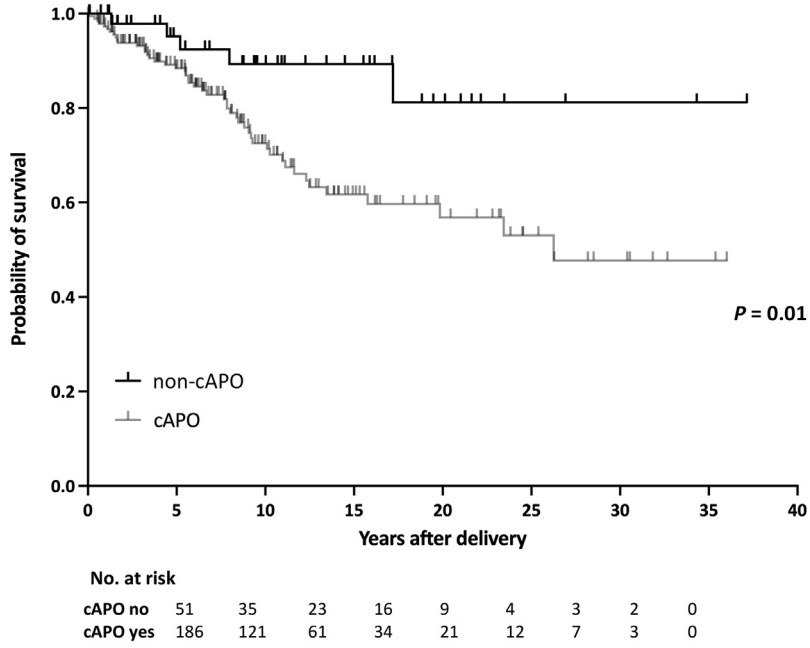

Figure 3 | Death-censored graft loss in years after delivery in kidney transplant recipients combined adverse pregnancy outcome (cAPO) versus non-cAPO (n = 237 pregnancies). Survival analysis, log-rank (Mantel-Cox) test.

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 lack of a proper definition for superimposed PE existing in women with CKD.

Second, although much effort was undertaken to carefully address missing values, missing data are a limitation of our study. Bias was introduced by the exclusion of pregnancies missing on the cAPO from prediction analysis. However, multiple imputation of missing predictor values did not suggest an imbalance in their distribution as compared with 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 analyzed. From our experiences (superimposed) PE, kidney 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 successful. Pregnancy outcomes sorted per prepregnancy eGFR-CKD category are helpful for individualized prepregnancy counseling. Independent predictors for adverse outcomes such as prepregnancy eGFR and (the absence of) midterm SCr and blood pressure drop help identifying high-risk pregnancies. This can help the clinician in optimizing the 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.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Baseline characteristics of twin pregnancies.
Table S2. Pregnancy outcomes of twin pregnancies.
Table S3. Use of antihypertensive medication during pregnancy.
Table S4. Use of immune suppressive medication before and during pregnancy.
Table S5. Baseline characteristics of pregnancies stratified per decennium.
Table S6. Pregnancy outcomes stratified per decennium.
Table S7. Baseline characteristics of pregnancies stratified per use of calcineurin inhibitor (CNI) (cyclosporine [CyA] and tacrolimus).
Table S8. Pregnancy outcomes stratified per use of calcineurin inhibitor (CNI) (cyclosporine [CyA] and tacrolimus).
Table S9. Combined adverse pregnancy outcome frequencies.
Table S10. Baseline characteristics of pregnancies in prediction analysis, $n = 237$.
Table S11. Baseline characteristics of pregnancies with and without missing outcome data.
Table S12. Potential predictors combined adverse pregnancy outcome (cAPO) before and after multiple imputation, $n = 237$.
Figure S1. Scatterplots for imputed predictors of the combined adverse pregnancy outcome. Each pregnancy is represented by a dot or square, $n = 237$.

REFERENCES

1. Murray JE, Reid DE, Harrison JH, Merrill JP. Successful pregnancies after human renal transplantation. *N Engl J Med*. 1963;269:341–343.
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*. 2016;44:321–327.
3. Hamilton BE, Martin JA, Ostermann MJK, et al. Births: provisional data for 2018 Vol. 004. Division of Vital Statistics; 2018. Accessed October 1, 2021. https://www.cdc.gov/nchs/data/vsrr/report004.pdf
4. Gill JS, Zalunardo N, Rose C, Tonelli M. The pregnancy rate and live birth rate in kidney transplant recipients. *Am J Transplant*. 2009;9:1541–1549.
5. Wyld ML, Clayton PA, Jesudason S, et al. Pregnancy outcomes for kidney transplant recipients. *Am J Transplant*. 2013;13:3173–3182.
6. Davison JM, Bailey DJ. Pregnancy following renal transplantation. *J Obstet Gynaecol Res*. 2003;29:227–233.
7. Wiles K, Webster P, Seed PT, et al. The impact of chronic kidney disease stages 3-5 on pregnancy outcomes. *Nephrol Dial Transplant*. 2021;36:2008–2017.
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*. 2013;8:290–298.
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*. 2016;30:673–681.
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*. 2017;31.
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*. 2014;85:49–61.
12. Shah S, Venkatesan RL, Gupta A, et al. Pregnancy outcomes in women with kidney transplant: metaanalysis and systematic review. *BMC Nephrol*. 2019;20:24.
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*. 2008;115:58–67.
14. American College of Obstetricians and Gynecologists, Women's Health Care Physicians. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 50, January 2003. *Obstet Gynecol*. 2004;103:203–216.

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*. 2010;55:622–627.
17. Hoftiezer L, Hukkelhoven CW, Hogeveen M, et al. Defining small-for-gestational-age: prescriptive versus descriptive birthweight standards. *Eur J Pediatr*. 2016;175:1047–1057.
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*. 2022;79:12–23.
20. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. 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.
21. Meddings J, Kerr EA, Heisler M, Hofer TP. 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*. 2012;12:270.
22. Webster K, Fishburn S, Maresh M, et al. 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;158:892–898.
24. Grindheim G, Estensen ME, Langesaeter E, et al. Changes in blood pressure during healthy pregnancy: a longitudinal cohort study. *J Hypertens*. 2012;30:342–350.
25. Clapp JF 3rd, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol*. 1997;80:1469–1473.
26. van Oppen AC, van der Tweel I, Alsbach GP, et al. A longitudinal study of maternal hemodynamics during normal pregnancy. *Obstet Gynecol*. 1996;88:40–46.
27. Ayala DE, Hermida RC, Mojón A, et al. Blood pressure variability during gestation in healthy and complicated pregnancies. *Hypertension*. 1997;30(Pt 2):611–618.
28. Lopes van Balen VA, Spaan JJ, Ghossein C, et al. Early pregnancy circulatory adaptation and recurrent hypertensive disease: an explorative study. *Reprod Sci*. 2013;20:1069–1074.
29. Sturgiss SN, Dunlop W, Davison JM. Renal haemodynamics and tubular function in human pregnancy. *Baillieres Clin Obstet Gynaecol*. 1994;8:209–234.
30. WHO. Preterm birth fact sheet. WHO; 2020. Accessed May 3, 2022. https://www.who.int/news-room/fact-sheets/detail/preterm-birth
31. WHO. Low birth weight indicator metadata registry details. WHO; 2020. Accessed May 3, 2022. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/76
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*. 2014;161:819–826.
33. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med*. 2015;372:407–417.
34. van Buren MC, Gosselink M, Groen H, et al. Effect of pregnancy on EGFR after kidney transplantation: a national cohort study. *Transplantation*. 2022;106:1262–1270.
35. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J Am Soc Nephrol*. 2009;20:2433–2440.
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*. 2018;31:665–681.
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*. 2021;34:2669–2679.
38. Sullivan TR, Lee KJ, Ryan P, Salter AB. Multiple imputation for handling missing outcome data when estimating the relative risk. *BMC Med Res Methodol*. 2017;17:134.
39. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant*. 2011;11:2388–2404.
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*. 2014;64:36–44.
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*. 2017;12:1048–1056.
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*. 2018;18:1158–1167.
43. Rose C, Gill J, Gill JS. Association of kidney transplantation with survival in patients with long dialysis exposure. *Clin J Am Soc Nephrol*. 2017;12:2024–2031.
44. Bailey P, Edwards A, Courtney AE. Living kidney donation. *BMJ*. 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*. 2000;70:625–631.
46. Mange KC, Feldman HI, Joffe MM, et al. Blood pressure and the survival of renal allografts from living donors. *J Am Soc Nephrol*. 2004;15:187–193.
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*. 2019;14:1642–1650.
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;35(Pt A):6492–6500.
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.
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 Med*. 2016;13:e1002018.
51. Piccoli GB, Cabiddu G, Attini R, et al. Risk of adverse pregnancy outcomes in women with CKD. *J Am Soc Nephrol*. 2015;26:2011–2022.
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;49:400–409.
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*. 2019;54:297–307.
54. Page EW, Christianson R. The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy. *Am J Obstet Gynecol*. 1976;125:740–746.
55. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ*. 2008;336:211–215.
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*. 2011;32:3088–3097.
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*. 2020;104:1675–1685.
58. Thompson BC, Kingdon EJ, Tuck SM, et al. Pregnancy in renal transplant recipients: the Royal Free Hospital experience. *QJM*. 2003;96:837–844.
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*. 2012;44:635–637.
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*. 2011;155:129–131.
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*. 2016;31:1957–1965.
62. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 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*. 2019;170:W1–W33.