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Pregnancy outcomes in women with kidney transplant: Metaanalysis and systematic review

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Abstract

Background: Reproductive function in women with end stage renal disease generally improves after kidney transplant. However, pregnancy remains challenging due to the risk of adverse clinical outcomes.

Methods: We searched PubMed/MEDLINE, Elsevier EMBASE, Scopus, BIOSIS Previews, ISI Science Citation Index Expanded, and the Cochrane Central Register of Controlled Trials from date of inception through August 2017 for studies reporting pregnancy with kidney transplant.

Results: Of 1343 unique studies, 87 met inclusion criteria, representing 6712 pregnancies in 4174 kidney transplant recipients. Mean maternal age was 29.6 \pm 2.4 years. The live-birth rate was 72.9% (95% Cl, 70.0–75.6). The rate of other pregnancy outcomes was as follows: induced abortions (12.4%; 95% Cl, 10.4–14.7), miscarriages (15.4%; 95% Cl, 13.8–17.2), stillbirths (5.1%; 95% Cl, 4.0–6.5), ectopic pregnancies (2.4%; 95% Cl, 1.5–3.7), preeclampsia (21.5%; 95% Cl, 18.5–24.9), gestational diabetes (5.7%; 95% Cl, 3.7–8.9), pregnancy induced hypertension (24.1%; 95% Cl, 18.1–31.5), cesarean section (62.6, 95% Cl 57.6–67.3), and preterm delivery was 43.1% (95% Cl, 38.7–47.6). Mean gestational age was 34.9 weeks, and mean birth weight was 2470 g. The 2–3-year interval following kidney transplant had higher neonatal mortality, and lower rates of live births as compared to > 3 year, and < 2-year interval. The rate of spontaneous abortion was higher in women with mean maternal age < 25 years and > 35 years as compared to women aged 25–34 years.

Conclusion: Although the outcome of live births is favorable, the risks of maternal and fetal complications are high in kidney transplant recipients and should be considered in patient counseling and clinical decision making.

Keywords: Pregnancy, Kidney transplant, Maternal, Fetal, Outcomes

Background

Women with end stage renal disease have impaired fertility due to disruption of hypothalamic gonadal axis. Pregnancy is therefore rare in women on dialysis with very low incidence of conception ranging from 0.9 to 7% [1]. Since there is rapid restoration of fertility, in some cases, within 6 months following transplantation, kidney transplantation offers the best hope to women with end-stage renal disease who wish to become pregnant [2].

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Pregnancy in a kidney transplant recipient continues to remain challenging due to risk of adverse maternal complications of preeclampsia and hypertension, and risk of adverse fetal outcomes of premature birth, low birth weight, and small for gestational age infants [3]. Additionally, there is risk of side effects from immunosuppressive medication, and risk of deterioration of allograft function [4]. Therefore, preconception counseling, family planning and contraception are pertinent parts of the transplant counseling process.

Data on clinical outcomes of pregnancy in kidney transplant recipients is limited from case reports, single-center studies, and voluntary registries. The use-fulness of the voluntary registries is further limited due to underreporting and incomplete data capture [5–8].

© The Author(s). 2019 **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated. To the best of our knowledge, no comprehensive metanalysis on post-kidney transplant pregnancy outcomes has been performed in the recent years [9]. Since kidney transplant is common in women of child bearing age and most of the data on outcomes of pregnancy comes from these retrospective studies, our metaanalysis is both timely and important. The comprehensive analysis of various worldwide registries, single-center studies, and case series will provide generalizable inferences about post-kidney transplant pregnancy outcomes, and help guide the pregnancy in kidney transplant recipients. The primary goal of this study was to perform a meta-analysis to systematically identify all studies of pregnancy-related outcomes in kidney transplant recipients from all around the world, and estimate pooled incidences of pregnancy outcomes, maternal complications, and fetal complications. The secondary goals were to examine the impact of pregnancy on the kidney allograft loss, allograft rejection, identify ideal maternal age of conception, and determine ideal time of conception between kidney transplant and pregnancy.

Methods

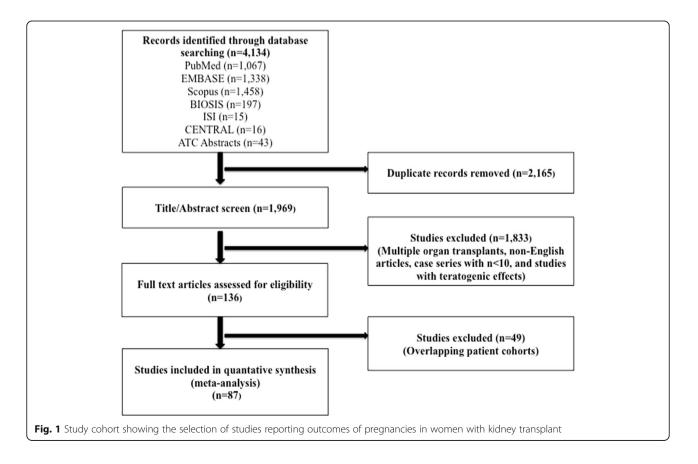
Data sources and searches

We performed a systematic review and meta-analyses reported according to PRISMA guidelines for studies exploring incidence and outcomes of pregnancy in

women with kidney transplant (Fig. 1). We searched PubMed/MEDLINE, Elsevier EMBASE, Scopus, BIOSIS Previews, ISI Science Citation Index Expanded, and the Cochrane Central Register of Controlled Trials (CEN-TRAL) from their earliest date of inception through 8/31/ 2017, and abstracts from the annual American Transplant Congresses from 1/1/2013 through 8/31/2017. A health sciences librarian (E.K.) developed database-specific search strategies including a combination of subject headings (MeSH or Emtree) and keywords. The following key search terms were used in strategies specific to each database and organization: pregnancy complications, pregnancy outcome, maternal outcome, fetal outcome, birth outcome, kidney transplant, or renal transplant. A reproducible PubMed search strategy is provided in Additional file 1.

Study selection

We considered observational studies (prospective cohort, retrospective cohort, and cross-sectional), case series, and case reports (with n > 10 pregnancies) that explored the pregnancy, maternal, and fetal outcomes among women ≥ 18 years, and who received a kidney transplant. Studies of patients with multiple organ transplants, studies that analyzed the teratogenic effects of



mycophenolate or sirolimus, and non–English language studies were excluded. Titles and abstracts of all identified citations were screened independently by two reviewers (S.S. and T.G.), who discarded studies that did not meet all inclusion criteria. The same reviewers independently screened the abstracts of all eligible studies. If eligibility was indeterminable from the abstract, the study was included in the full-text screen. All disagreements were adjudicated by the principal investigator (S.S).

Data extraction, quality assessment, and outcomes

Data extraction was carried out independently by three data extraction team members (A.G, L.R. and M.S.) using standard data extraction forms. Data elements were then rechecked for accuracy by all the three data extraction team members. When more than one publication of a similar patient population existed with more than 25% overlap, publication with higher number of pregnancy events and the most complete details was included. Disagreements in data extraction and quality assessment were resolved in consultation with an arbitrator (T.G.) and primary investigator (S.S.). For each included study, the following data was extracted: country of location, years of data collection, number of kidney transplant recipients, number of pregnancies, mean maternal age, mean interval between kidney transplant and pregnancy, pregnancy outcomes (number of live births, miscarriage, induced abortion, still birth and ectopic pregnancies), maternal outcomes (number of women with preeclampsia, pregnancy induced hypertension, and gestational diabetes mellitus, and number of cesarean sections), fetal outcomes (number of pre-term births, mean gestational age, mean gestational weight, and number of neonatal deaths); and graft outcomes (number of acute rejection during pregnancy, graft failure post pregnancy, mean serum creatinine pre and post pregnancy). To maintain consistency across extracted data, the number of pregnancies was used as a denominator for the outcomes of live births, miscarriages, induced abortions, stillbirths, neonatal deaths, preeclampsia, pregnancy induced hypertension, and gestational diabetes mellitus. The number of live births was used as the denominator for the outcome of preterm deliveries, and cesarean section. Preterm was defined as babies born alive before 37 weeks gestation.

Data synthesis and analysis

Patients characteristics were reported as frequencies. The pregnancy incidence was reported for women per 1000 live births. For each study, estimates were expressed as prevalence and 95% confidence intervals (CI). Prevalence estimates from individual studies were pooled using a random-effects model. Heterogeneity across included studies was analyzed formally using Cochran Q (heterogeneity 2) and I2 statistics. For binary outcomes, the DerSimonian-Laird method was used, and for continuous outcomes, a weighted average methodology was used to calculate the pooled estimates and 95% CI. Two-sample test of proportions was used to compare the pooled incidence for each analysis to the most recent United States (US) general population incidence. [10–14] We determined the associations of maternal age, the interval between kidney transplant, and the pregnancy outcomes. Additonally, we performed a subgroup analysis for the pregnancy, maternal and fetal outcomes for studies published from 2000 to 2017. Analyses were performed using MS Excel and Comprehensive Meta-analysis packages in R software.

Results

Among the 4134 citations that were retrieved, 136 full-text articles were reviewed and 87 were selected to be included in the final study cohort (Fig. 1). Three studies were from Africa, 31 from Asia, 31 from Europe, 10 from North America, 4 from Oceania, and 8 from South America (Table 1). Overall, there were 6712 pregnancies in 4174 kidney transplant recipients. Mean maternal age was 29.6 ± 2.4 years and mean interval between kidney transplant and pregnancy was 3.7 years.

Pregnancy outcomes

Live birth rate was 72.9% (95% CI, 70.0-75.6), miscarriages rate was 15.4% (95% CI, 13.8-17.2), induced abortions rate was 12.4% (95% CI, 10.4-14.7), stillbirths rate was 5.1% (95% CI, 4.0-6.5) and rate of ectopic pregnancies was 2.4% (95% CI, 1.5-3.7). In our study cohort of kidney transplant recipients, live birth rates were higher as compared to the US general population (72.9% vs. 62%) and favorable across all geographic regions (Fig. 2) [10, 11]. Overall, miscarriage rate was slightly lower than that of the US general population (15.4% vs. 17.1%), but higher across Africa (21.0%; 95% CI, 14.3-29.9), and South America (20.2%; 95% CI, 15.6–25.7) (Fig. 3) [13]. Induced abortion rate was also lower than the US general population (12.4% vs. 18.6%) [13]. The rate of induced abortion was highest in South America (19.8%; 95% CI, 12.2-30.3), followed by Asia (13.3%; 95% CI, 9.6-18.3), Oceania (11.5%; 95% CI, 9.3-14.0), North America (10.9%; 95% CI, 5.9-19.2), Europe (10.0%; 95% CI, 7.3-13.5), and Africa (7.7, 95% CI, 1.4-32.6) (Fig. 4). Overall, stillbirth rate was higher than the US general population (5.1% vs. 0.6%) [14]. Worldwide, stillbirth rate was highest in Asia (6.6, 95% CI, 4.8-9.0%), and lowest in Africa (2.6, 95% CI; 0.4-16.5) (Fig. 5). The rate of ectopic pregnancy was slightly higher than the US general population (2.4% vs. 1.4%), with highest rate in Asia (3.3, 95% CI; 1.1–9.8) (Fig. 6) [15]. The results from the subgroup analyses (2000-2017) for pregnancy

Table 1 Studies included in the metaanalysis

	Reference, Year Published	Study Years	Country	Recipients	Pregnancies
1	Devresse et al., 2017 [32]	1994–2010	Belgium	32	57
2	Yuksel et al., 2017 [33]	2009–2016	Turkey	25	na
3	Ajaimy et al., 2016 [34]	2009–2014	USA	11	11
1	Candido et al., 2016 [35]	2004-2014	Portugal	36	53
5	Cristelli et al., 2016 [36]	2004-2014	Brazil	36	53
5	El Houssni et al., 2016 [37]	na	Saudi Arabia	12	21
7	Lima et al., 2016 [38]	2004-2014	Brazil	36	53
3	Majak et al., 2016 [39]	1969–2013	Norway	na	119
9	Mishra et al., 2016 [40]	2004-2014	India	16	na
10	Orihuela et al., 2016 [41]	1986–2014	Uruguay	32	40
11	Piccoli et al., 2016 [42]	1978–2013	Italy	na	189
12	Saliem et al., 2016 [43]	2006-2011	Canada	na	264
13	Santos et al., 2016 [44]	2010-2014	Portugal	8	8
14	Sarween et al., 2016 [45]	2001-2015	UK	387	569
15	Stoumpos et al., 2016 [46]	1973–2013	UK	89	138
16	Yoshikawa et al., 2016 [47]	na	Japan	49	65
17	Aktrurk et al., 2015 [48]	2004-2014	Turkey	12	16
18	Arab et al., 2015 [49]	2003-2010	Canada	na	375
19	Erman et al., 2015 [50]	1987-2011	Turkey	43	43
20	Yeon et al., 2015 [51]	1995-2015	Korea	84	119
21	Debska – Slizien et al., 2014 [52]	1980-2012	Poland	17	22
22	Farr et al., 2014 [53]	1999–2013	Austria	12	12
23	Hebral et al., 2014 [54]	1969-2011	France	46	61
24	You et al., 2014 [55]	1995-2013	Korea	29	41
25	Blume et al., 2013 [56]	1988–2010	Germany	34	53
26	Guella et al., 2013 [57]	1992-2008	Saudi Arabia	15	33
27	Pietrzak et al., 2013 [58]	2001-2012	Poland	34	40
28	Rachdi et al., 2013 [59]	2003-2013	Tunisia	12	17
29	Ribeiro et al., 2013 [60]	1995-2007	Brazil	22	31
30	Rocha et al., 2013 [61]	1983-2009	Portugal	24	25
31	Wyld et al., 2013 [62]	1971-2010	Australia	447	692
32	Kennedy et al., 2012 [63]	na	Ireland	18	29
33	Neyatani et al., 2012 [64]	1975-2011	Japan	22	34
34	Van Buren et al., 2012 [65]	1971-2010	Netherlands	30	42
35	Celik et al., 2011 [66]	1998-2008	Turkey	24	31
36	Gerlei et al., 2011 [67]	1974–2010	Hungary	23	27
37	Lopez et al., 2011 [68]	1986-2010	Spain	20	24
38	Xu et al., 2011 [69]	1989–2008	China	25	38
39	Gorgulu et al., 2010 [70]	1983–2008	Turkey	19	22
40	Areia et al., 2009 [71]	1989–2007	Portugal	28	34
41	Gill et al., 2009 [20]	1990–2003	USA	483	530
42	Levidiotis et al., 2009 [8]	1966–2005	Australia	381	577
43	Rizvi et al., 2009 [72]	1985-2008	Pakistan	45	72
44	Sharma et al., 2009 [73]	1988–2006	Oman	42	82

Table 1 Studies included in the metaanalysis (Continued)

-	Reference, Year Published	Study Years	Country	Recipients	Pregnancies
45	Al Duraihimh et al., 2008 [74]	1996-2006	Middle East	140	234
46	Alfi A Yet al, 2008 [75]	1989–2005	Saudi Arabia	12	20
47	Cruz Lemini et al., 2007 [28]	1990–2005	Mexico	60	75
48	Oliveira et al., 2007 [76]	2001-2005	Brazil	52	52
49	Sibanda et al., 2007 [77]	1994-2001	UK	176	193
50	Yassaee et al., 2007 [78]	1996-2001	Iran	74	95
51	Kurata et al., 2006 [79]	1984–2003	Japan	42	53
52	Rahamimov et al., 2006 [80]	1983–1998	Israel	39	69
53	Galdo et al., 2005 [81]	1982-2002	Chile	30	37
54	Garcia - Donaire et al., 2005 [82]	1997-2004	Spain	16	19
55	Ghanem et al., 2005 [83]	1989–2004	Egypt	41	67
56	Pour-Reza-Gholi et al., 2005 [84]	1984–2004	Iran	60	74
57	Yildirim et al., 2005 [85]	1998–2005	Turkey	17	20
58	Keitel et al., 2004 [86]	1977-2001	Brazil	41	44
59	Pezeshki et al., 2004 [87]	1991–1998	Iran	18	20
60	Hooi et al., 2003 [88]	1984-2001	Malaysia	46	72
61	Queipo et al., 2003 [89]	1980–2000	Spain	29	40
62	Thompson et al., 2003 [90]	1976-2001	UK	24	48
63	Sgro et a,l 2002 [91]	1988–1998	Canada	26	44
64	Tan et al., 2002 [92]	1986–2000	Singapore	25	42
65	Park et al., 2001 [93]	na - 2000	South Korea	36	47
66	Kuvacic et al., 2000 [94]	1986–1996	Croatia	15	23
67	Little et al., 2000 [27]	1985–1998	Ireland	19	29
68	Moon et al., 2000 [95]	na - 1998	Korea	36	48
69	Ventura et al., 2000 [96]	1983–1999	Portugal	15	15
70	Arsan et al., 1997 [97]	na	France	20	33
71	Rahbar et al., 1997 [98]	1985–1993	Iran	13	14
72	Rieu et al., 1997 [99]	1970–1995	France	22	33
73	Al Hassani et al., 1995 [100]	1985–1993	Oman	25	44
74	Sabagh et al., 1995 [101]	1984–1994	Saudi Arabia	33	52
75	Saber et al., 1995 [102]	1968–1992	Brazil	19	25
76	Wong et al., 1995 [103]	1972–1992	New Zealand	9	16
77	Hadi et al., 1986 [104]	1969–1992	South Korea	11	13
78	Talaat et al., 1994 [105]	1977–1992	Sweden	19	25
79	Pahl et al., 1993 [106]	1969–1990	USA	21	32
80	Muirhead et al., 1992 [107]	1977–1988	UK	22	22
81	Brown et al., 1991 [108]	1965-1989	Ireland	14	27
82	Sturgiss et al., 1991 [109]	1967–1987	UK	17	22
83	O' Connell et al., 1989 [110]	1974–1986	Australia	11	18
84	Ha et al., 1994 [111]	1970–1982	USA	13	17
85	Marushak et al., 1986 [112]	1972–1983	Denmark	20	24
86	O' Donnell et al., 1985 [113]	1971–1984	South Africa	21	38
87	Waltzer et al., 1980 [114]	na	USA	12	15

		anong nau	ney Transplant Ro		
Paper Live Bi	rths, n Pregn	ancies, n	L	ive Births, % 95%	C.I Weig
Africa			3		
O' Donnell 1985 Rachdi 2013	22 16	38 17		57.895 [41.933; 94.118 [67.968;	
Random effects model	10	55		79.430 [26.433; 9	
Heterogeneity/ $\hat{r} = 81\%$, $\tau^2 = 2.4262$, $\chi_1^2 = 5.1$	5 (p = 0.02)			15.400 [20.400, 5	
Asia					
Aktrurk - 2015	11	16		68.750 [43.323;	
Al Duraihimh 2008 Al Hassani 1995	174 31	234 44		74.359 [68.380; 70.455 [55.513;	
Alfi A Y 2008	20	20	:	70.455 [55.513; 100.000 [71.262;	
Celik 2011	23	31		74.194 [56.256;	86.536]
Neyatani 2012	17	34		50.000 [33.799;	
Park 2001	25 17	47 20		53.191 [39.052;	
Pezeshki 2004 El Houssni 2016	16	20		85.000 [62.416; 76.190 [53.966;	
Erman Akar 2015	29	43		67.442 [52.258;	
Guella 2013	21	33	_	63.636 [46.266;	
Hau 1994	7	13		53.846 [28.165;	77.636]
Hooi 2003	49	72		68.056 [56.486;	77.760]
Pour 2005	32	74	;	43.243 [32.479;	
Rahamimov 2006 Rahbar 1997	55 11	69 14		79.710 [68.602; 78.571 [50.567;	
Sabagh 1995	44	14 52		78.571 [50.567; 84.615 [72.140;	
Sharma 2009	58	82		70.732 [60.029;	79.545]
Tan 2002	29	42		69.048 [53.697;	81.100]
Xu 2011	25	38		65.789 [49.593;	78.987]
Yassaee 2007	72	95		75.789 [66.189;	
Yeon 2015 Yildirim 2005	84 16	119 20		70.588 [61.802; 80.000 [57.215;	
You 2014	30	41		73.171 [57.748;	
Moon 2000	26	48	_ _	54.167 [40.114;	
Random effects model Heterogeneity/ 2 = 01%, τ^2 = 0.1555, χ^2_{24} = 02	2.28 (p < 0.01)	1322	-	69.057 [64.394; 7	
-					
Europe Areia 2009	27	34		79.412 [62.683;	90 9551
Arsan 1997	25	33		75.758 [58.499;	
Blume 2013	32	53	_ _	60.377 [46.774;	
Brown 1991	23	27		85.185 [66.539;	
Candido 2016	41	53		77.358 [64.230;	
Debska - Slizien 2014	17	22		77.273 [55.642;	
Devresse 2017 Farr 2014	43 12	57 12	<u> </u>	75.439 [62.692; 100.000 [59.681;	
Garcia 2005	12	12		100.000 [59.081, 100.000 [70.192;	
Gerlei 2011	27	27		100.000 [77.038;	99.889]
Hebral 2014	57	61		93.443 [83.794;	97.517]
Kennedy 2012	23	29		79.310 [60.951;	
Kuvacic 2000 Queipo 2003	15 28	23 40		65.217 [44.289; 70.000 [54.266;	
Rieu 1997	32	33	:	96.970 [81.387;	
Santos 2016	7	8		87.500 [46.272;	
Sarween 2016	390	569	=	68.541 [64.607;	72.226]
Sibanda 2007	153	193	-	79.275 [72.978;	
Stoumpos 2016	102	138 22		73.913 [65.960; 72.727 [51.064;	
Sturgiss 1991 Thompson 2003	16 32	22 48		72.727 [51.064; 66.667 [52.324;	
Van Buren 2012	41	40		97.619 [84.939;	
Ventura 2000	11	15	_	73.333 [46.686;	89.623]
Little 2000	23	29		79.310 [60.951;	90.398]
Lopez 2011	18	24		75.000 [54.356;	
Marushak 1986 Random effects model	24	24 1635	-	100.000 [74.873; 77.461 [73.124; 8	99.876] 3 1.278] 3
Heterogeneity/ $\hat{\tau}$ = 58%, τ^{2} = 0.1514, χ^{2}_{25} = 58	0.12 (p < 0.01)	1000	-	11.401 [13.124; 0	
North America					
Criuz lemini 2007	64	75	: _ _	85.333 [75.422;	91.688]
Pahl 1993	26	32		81.250 [64.076;	
Sgro 2002	32	44	÷	72.727 [57.869;	
Waltzer 1980	11	15		73.333 [46.686;	
Gill 2009 Random effects model	294	530 696		55.472 [51.211; 74.119 [57.567; 8	
Heterogeneity/ = 87%, τ^2 = 0.5877, χ^2_4 = 31.	22 (p < 0.01)	030		14.119 [01.001; 0	
Oceania					
O'Connell 1989	10	18	_	55.556 [33.036;	76.0031
Levidiotis 2009	444	577	÷ •	76.950 [73.336;	
Wong 1995	11	16		68.750 [43.323;	86.361]
Wyld 2013	526	692		76.012 [72.688;	
Random effects model Heterogeneity/ ² = 35%, τ ² = 0.0127, χ ₃ ² = 4.5	8 (p = 0.21)	1303	*	75.501 [71.709; 7	78.935]
South America Orihuela 2016	29	40	<u> </u>	72.500 [56.841;	84.0701
Keitel 2004	27	44	_	61.364 [46.401;	
Saber 1995	21	25	-	84.000 [64.313;	93.863]
Random effects model		109		71.374 [57.507; 8	32.123]
Heterogeneity/ [*] = 48%, τ [*] = 0.1401, χ [*] ₂ = 3.8	7 (p = 0.14)				
Overall Effect Heterogeneity/ ² = 72%, τ^{2} = 0.1791, $\chi^{2}_{e_{4}}$ = 22		5120	· · · · · · · · · · · · · · · · · · ·	72.914 [70.008; 7	75.637] 100

						Mean verall Value
	Miscarriage a	amona Ki	dnev Transr	plant Recipients		
Paper	Miscarriage, n Preg	-		Miscarriage, %	95% C.I	Weight
Africa	3, 3	,	:	3,		5
O' Donnell 1985	9	38	֥	23.684	[12.809; 39.599]	2.19
Ghanem 2005	13	67		19.403	[11.614; 30.608]	2.89
Random effects model Heterogeneity/ $\hat{\tau} = 0\%$, $\tau^2 = 0$, χ^2		105		21.024	[14.257; 29.883]	4.9%
	0.2. (0 0.00)					
Asia Aktrurk - 2015	4	16		25.000	[9.707; 50.824]	1.19
Al Duraihimh 2008	45	234	-	19.231	[14.677; 24.787]	5.09
Al Hassani 1995	5	44		11.364	[4.810; 24.544]	1.59
Alfi A Y 2008	0	20	► <u>−</u>	0.000	[0.147; 28.738]	0.29
Neyatani 2012	8	34		23.529	[12.227; 40.462]	1.99
Park 2001	4	47		8.511	[3.231; 20.581]	1.39
Pezeshki 2004	1	20		5.000	[0.700; 28.220]	0.49
Erman Akar 2015	10	43	· · ·	23.256	[12.995; 38.074]	2.39
Hooi 2003	11	72		15.278	[8.667; 25.522]	2.69
Rahbar 1997	1 9	14		7.143	[0.996; 37.028]	0.49
Rizvi 2009 Sabagh 1995	9	72 52		12.500 9.615	[6.634; 22.314] [4.059; 21.103]	2.39 1.59
Sharma 2009	5 11	52 82		13.415	[7.587; 22.623]	2.69
Tan 2002	7	42		16.667	[8.159; 31.047]	1.99
Xu 2011	7	38	┝╌╎╌┝╶┾╶╎╴┿╌╎╴┿╶┝╶┝╶┝╶┝╴┝╴┝	18.421	[9.044; 33.897]	1.89
Yassaee 2007	16	95	-	16.842	[10.582; 25.740]	3.29
Yeon 2015	16	119		13.445	[8.403; 20.826]	3.39
Yildirim 2005	1	20		5.000	[0.700; 28.220]	0.49
Moon 2000	8	48		16.667	[8.560; 29.936]	2.09
Random effects model Heterogeneity/ $^{2} = 0\%$, $\tau^{2} = 0$, χ^{2}		1112	1	15.983	[13.890; 18.324]	35.5%
Furana						
Europe Areia 2009	3	34	_	8.824	[2.874; 24.043]	1.09
Arsan 1997	5	33		15.152	[6.450; 31.622]	1.49
Blume 2013	13	53		24.528	[14.809; 37.796]	2.79
Candido 2016	9	53	- +	16.981	[9.079; 29.527]	2.29
Debska - Slizien 2014	2	22		9.091	[2.284; 29.963]	0.79
Devresse 2017	9	57		15.789	[8.425; 27.647]	2.29
Hebral 2014	1	61	-	1.639	[0.230; 10.735]	0.49
Kennedy 2012	4	29		13.793	[5.275; 31.494]	1.29
Sarween 2016 Sibanda 2007	103 22	569 193		18.102 11.399	[15.150; 21.483]	6.19 3.99
Stoumpos 2016	22	138		16.667	[7.624; 16.705] [11.333; 23.835]	3.99
Thompson 2003	6	48		12.500	[5.725; 25.152]	1.79
Little 2000	4	29	┿╪╪ ┿╵┿╵┼┿╵ ┺	13.793	[5.275; 31.494]	1.29
Lopez 2011	4	24	- +	16.667	[6.399; 36.914]	1.29
Random effects model Heterogeneity/ ² = 20%, τ ² = 0.0		1343	1	15.493	[13.054; 18.292]	29.8%
North America Ajaimy 2016	2	11		18.182	[4.581; 50.702]	0.69
Criuz lemini 2007	10	75		13.333	[7.327; 23.040]	2.59
Pahl 1993	1	32		3.125	[0.438; 19.113]	0.49
Sgro 2002	6	44		13.636	[6.257; 27.194]	1.79
Waltzer 1980	0	15		0.000	[0.193; 35.028]	0.29
Gill 2009	92	530		17.358	[14.366; 20.823]	6.09
Random effects model Heterogeneity/ ² = 15%, τ ² = 0.0		707	Ť	15.202	[11.537; 19.773]	11.49
Oceania						
O' Connell 1989	1	18		5.556	[0.777; 30.652]	0.49
Wong 1995	3	16		18.750	[6.170; 44.746]	0.99
Wyld 2013	60	692		8.671	[6.791; 11.009]	5.69
Random effects model Heterogeneity/ ² = 4%, τ ² = 0.01		726	•	9.056	[6.658; 12.206]	6.9%
South America						
Cristelli 2016	12	53		22.642	[13.332; 35.770]	2.69
Orihuela 2016	10	40	÷-•	25.000	[14.012; 40.542]	2.29
Galdo 2005	7	37		18.919	[9.296; 34.692]	1.89
Keitel 2004	6	44		13.636	[6.257; 27.194]	1.79
Saber 1995	2	25		8.000	[2.009; 26.944]	0.79
Lima 2016	12	53		22.642	[13.332; 35.770]	2.69
Random effects model Heterogeneity/ $^2 = 0\%$, $\tau^2 = 0$, χ^2_3		252		20.152	[15.557; 25.693]	11.69
Overall Effect		4245		15 412	[13.819; 17.151]	100.0%
Heterogeneity/ 2 = 38%, τ^2 = 0.0	578, $\chi^2_{10} = 76.95 (p < 0.01)$	4243		15.412	13.019, 17.191]	100.05
			0 20 40 60	0 80 100		
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Wong 1995 2 16 12.500 [3.145; 38.596] Wyld 2013 78 692 11.272 [9.122; 13.851] Random effects model 726 11.455 [9.332; 13.987] Heterogeneity ⁷ = 0%, ² = 0.51 (p = 0.77) 726 11.455 [9.332; 13.987] South America Keitel 2004 10 44 22.727 [12.688; 37.316] Ribeiro 2013 7 31 22.581 [11.164; 40.367]		-	3 12		16 667 [5 473· 40	858] 1.5%
Wyld 2013 78 692 11.272 [9.122; 13.851] Random effects model 726 11.455 [9.332; 13.987] Heterogeneity/ ⁵ = 0%, t ² = 0.51 (p = 0.77) 726 11.455 [9.332; 13.987] South America 22.727 [12.688; 37.316] Ribeiro 2013 7 31 22.581 [11.164; 40.367]						
Random effects model 726 11.455 [9.332; 13.987] Heterogeneity ⁷ = 0%, t ² = 0.751 9.32; 13.987] South America 22.727 [12.688; 37.316] Keitel 2004 10 44 Tobeiro 2013 7 31						
South America Keitel 2004 10 44 – 22.727 [12.688: 37.316] Ribeiro 2013 7 31 – 22.581 [11.164; 40.367]	ndom effects model			•		
Keitel 2004 10 44 22.727 [12.688; 37.316] Ribeiro 2013 7 31 ■ 22.581 [11.164; 40.367]		0.51 (p = 0.77)				
Ribeiro 2013 7 31 22.581 [11.164; 40.367]		40) 44		70 707 110 600 77	316] 2.6%
0,000 [2,009,20,944]					8.000 [2.009; 26.	
Random effects model 100 19.754 [12.233; 30.303] Heterogeneity/ ² = 16%, t ² = 0.0435, y ² ₂ = 2.38 (p = 0.30)	ndom effects model		100	-		
				_	12.388 [10.396: 14.1	599] 100.0%
$\begin{array}{c} + 7.0 \\ \text{Heterogeneity}^{2} = 65\%, \tau^{2} = 0.2809, \chi^{2}_{53} = 151.14 \ (p < 0.01) \\ 0 \ 20 \ 40 \ 60 \ 80 \ 100 \\ \end{array}$	erogeneity/ = 65%, τ ² = 0.26	9. $\chi_{53}^2 = 151.14 \ (p < 0)$	0.01)	0 20 40		

C+i	II Dirth on	oona Ki	dnov Tranon	ant Paginianta	L	verall Value
		-	uney transp	ant Recipients		
-	Birth, n Live E	Births, n		Still Birth, %	95% C.I	Weight
Africa O' Donnell 1985	1	38	÷	2.632	[0.369; 16.457]	1.3
Random effects model Heterogeneitynot applicable		38	-	2.632 [0.369; 16.457]	1.3
Asia						
Al Duraihimh 2008 Al Hassani 1995	17 3	234 44	-	7.265 6.818	[4.564; 11.374] [2.216; 19.113]	3.9 2.4
Alfi A Y 2008	õ	20		0.000	[0.147; 28.738]	0.7
Celik 2011	2	31		6.452	[1.619; 22.422]	1.9
El Houssni 2016 Erman Akar 2015	2 1	21 43		9.524 2.326	[2.393; 31.125] [0.327; 14.748]	1.9 1.3
Gorgulu 2010	0	22		0.000	[0.135; 26.811]	0.7
Guella 2013	2	33		6.061	[1.521; 21.233]	1.9
Hau 1994	1	13		7.692	[1.072; 39.057]	1.2
Hooi 2003 Pour 2005	2 7	72 74	-	2.778 9.459	[0.696; 10.435] [4.577; 18.539]	2.0 3.2
Rahamimov 2006	0	69		0.000	[0.045; 10.408]	0.7
Rahbar 1997	1	14	1	7.143	[0.996; 37.028]	1.2
Rizvi 2009 Sabagh 1995	5 2	72 52	-	6.944 3.846	[2.920; 15.622] [0.964; 14.118]	2.9
Sharma 2009	7	82)- 	8.537	[4.124; 16.840]	3.2
Tan 2002	1	42	<u>+</u>	2.381	[0.334; 15.061]	1.3
Yassaee 2007 Yildirim 2005	2 0	95 20		2.105 0.000	[0.527; 8.027] [0.147; 28.738]	2.0
You 2014	9	41	·	21.951	[11.836; 37.075]	3.3
Random effects model Heterogeneity/ ² = 28%, τ ² = 0.1371, χ ² ₁₉ =	26.25 (p = 0.12)	1094	•	6.610 [4.825; 8.995]	38.5
Europe						
Areia 2009	2	34		5.882	[1.476; 20.685]	1.9
Brown 1991 Candido 2016	1 3	27 53		3.704 5.660	[0.519; 22.084] [1.837; 16.133]	1.3
Debska - Slizien 2014	2	22		9.091	[2.284; 29.963]	1.9
Devresse 2017	1	57	-	1.754	[0.247; 11.426]	1.3
Gerlei 2011	0	27		0.000	[0.111; 22.962]	0.7
Kennedy 2012 Queipo 2003	4	29 40		13.793 7.500	[5.275; 31.494] [2.439; 20.821]	2.6 2.4
Rieu 1997	1	33	•	3.030	[0.425; 18.613]	1.3
Rocha 2013	0	25	-	0.000	[0.119; 24.361]	0.7
Sibanda 2007 Stoumpos 2016	6 2	193 138		3.109 1.449	[1.403; 6.745] [0.363; 5.607]	3.1
Sturgiss 1991	5	22		22.727	[9.789; 44.358]	2.7
Thompson 2003	2	48	*	4.167	[1.044; 15.190]	2.0
Van Buren 2012 Ventura 2000	1 1	42 15		2.381 6.667	[0.334; 15.061] [0.931; 35.199]	1.3
Little 2000	2	29		6.897	[1.731; 23.751]	1.2
Marushak 1986	ō	24	+	0.000	[0.124; 25.127]	0.7
Random effects model Heterogeneity/ \hat{r} = 32%, τ^{2} = 0.2537, χ^{2}_{17} =	25.01 (p = 0.09)	858	•	5.353 [3.556; 7.983]	31.4
North America			_		14.064-40.057	
Ajaimy 2016 Pahl 1993	1 1	11 32		9.091 3.125	[1.264; 43.857] [0.438; 19.113]	1.2
Hadi 1986	0	17	•	0.000	[0.172; 32.208]	0.7
Sgro 2002	4	44		9.091	[3.454; 21.844]	2.7
Muirhead 1992 Gill 2009	1 8	22 530		4.545 1.509	[0.636; 26.145] [0.757; 2.989]	1.2 3.4
Random effects model Heterogeneity $\hat{r} = 52\%$, $\tau^2 = 0.5568$, $\chi^2_e = 1$		656	-		1.655; 8.995]	10.5
O' Connell 1989	5	18	_ _	27.778	[12.058; 51.896]	2.7
Levidiotis 2009	12	577		2.080	[1.185; 3.626]	3.7
Wyld 2013 Random effects model	18	692 1287	·	2.601 5.219 [[1.645; 4.090] 1.465; 16.934]	3.9 10.3
Heterogeneity/ 2 = 92%, τ^{2} = 1.2052, χ^{2}_{2} = 2	24.84 (p < 0.01)	.207		0.219 [10.0
South America Cristelli 2016	3	53		5.660	[1 837: 16 132]	2.4
Orihuela 2016	3	40	⊷	2.500	[1.837; 16.133] [0.351; 15.728]	2.4
Keitel 2004	1	44	+	2.273	[0.319; 14.448]	1.3
Saber 1995 Lima 2016	1 2	25 53	-	4.000	[0.561; 23.547]	1.2
Elima 2016 Random effects model Heterogeneityi ² = 0%, τ^2 = 0, χ^2_a = 0.94 (p		215	-	3.774 3.936 [[0.946; 13.873] [1.979; 7.678]	2.0 8.1
Heterogeneity = 0%, $t = 0, \chi_4 = 0.94$ (p Overall Effect		4148		5.004 5	3.960; 6.524]	100.0
Heterogeneity/ 2 = 53%, τ^{2} = 0.4024, χ^{2}_{52} =	109.86 (p < 0.01)	4140	0 20 40 60	80 100	0.000, 0.024	100.0

	Ectopic Fit	gnancy ar	nong Ki	aney	Tran	spia	nt Recipients			
Paper	Ectopic Pregnancy, n	Pregnancies,	n				Ectopic Pregnancy, %	95%	C.I	Weight
Asia										
Al Hassani 1995		0	44	•			0.000	[0.069;	15.430]	2.8
Alfi A Y 2008			20	•			0.000		28.738]	2.8
Tan 2002			42	÷			4.762			9.8
Random effects model		1	06	-			3.316	[1.071;	9.803]	15.5
Heterogeneity/ ² = 0%, τ^2 = 0, χ^2_2	= 0.94 (p = 0.62)									
Europe										
Devresse 2017		2	57	+			3.509	[0.879;	12.973]	10.0
Gerlei 2011		0	27	-	-		0.000	[0.111;	22.962]	2.8
Sarween 2016		0 5	69				0.000	[0.005	; 1.386]	2.9
Sibanda 2007			93	÷			0.518	[0.073	3.583]	5.5
Stoumpos 2016		3 1	38	+			2.174	[0.703	6.522]	14.2
Thompson 2003		2	48	÷			4.167	[1.044;	15.190]	9.9
Random effects model		10	32	+			1.677	[0.673;	4.118]	45.2
Heterogeneity/² = 42%, τ² = 0.52	84. $\chi_5^2 = 8.58 \ (p = 0.13)$							•	-	
North America										
Gill 2009	1	4 5	30				2.642	[1.571	: 4.410]	39.3
Random effects model		5	30	•			2.642	[1.571;	4.410	39.3
Heterogeneitynot applicable										
Overall Effect		16	68	4			2.351	[1.471;	3 7351	100.0
Heterogeneity/ 2 = 13%, τ^2 = 0.07	74 - A - A - A - A - A - A - A - A - A -	10						[1.471,	J./ JJ	700.0

outcomes were consistent with the current findings (Additional file 2).

Maternal outcomes

Overall, rates of preeclampsia was 21.5% (95% CI, 18.5-24.9; US mean, 3.8%), cesarean section was 62.6% (95% CI, 57.6-67.3; US mean, 31.9%), gestational diabetes was 5.7% (95% CI, 3.7-8.9; US mean, 9.2%), and pregnancy induced hypertension was 24.1% (95% CI, 18.1-31.5). [12, 16] Preeclampsia rate was highest in Oceania (27.0%; 95% CI, 23.6-30.8), followed by North America (25.5%; 95% CI, 14.5-40.8), and lowest in Africa (10.5%; 95% CI, 4.0-24.9%) (Fig. 7). Cesarean section rate was highest in South America (88.8%; 95% CI, 49.3-98.5), followed by Africa (77.5%; 95% CI, 6.3-99.4) (Fig. 8). Worldwide, Oceania had the lowest rates of gestational diabetes (1.0%; 95% CI, 0.5-2.3%) (Fig. 9). With regards to pregnancy induced hypertension, highest rate was reported in South America (48.0, 95% CI, 15.1-82.7), while lowest rate was in Africa (16.1, 95% CI, 9–26.9) (Fig. 10). The results from the subgroup analyses (2000–2017) for maternal outcomes were consistent with the current findings (Additional file 2).

Fetal outcomes

Overall, rate of preterm birth was 43.1% (95% CI, 38.7-47.6) defined by babies born alive before 37 weeks of gestation, and neonatal mortality was 3.8% (95% CI, 2.8-5.2). Rates of preterm birth was highest in South America (55.0%), and lowest in North America (35.4%) (Fig. 11). The mean gestational age for newborns was 34.9 weeks (US mean, 38.7 weeks) and the mean birth weight was 2470 g (US mean, 3389 g). [12, 17] Neonatal mortality was high across all geographical regions as compared to the US mean (3.8% vs. 0.4%), with highest rate in Africa (18.4%; 95% CI, 9.1-33.9) and lowest rate in North America (1.3, 95% CI, 0.2–8.9) (Fig. 12) [18]. The results from the subgroup analyses (2000-2017) for fetal outcomes were consistent with the present findings except for neonatal mortality which was slighly lower in the subgroup analysis (2.9% vs. 3.8%) (Additional file 2).

Graft outcomes

The overall acute rejection rate during pregnancy among 822 kidney transplant recipients was 9.4% (95% CI, 6.4–13.7), which was comparable to the US mean of 9.1%. [19] Rates of acute renal allograft rejection were highest in Asia (11.0%), followed by South America (10.7%), Oceania (9.1%), Europe (7.3%), North America (6.7%), and Africa (4.8%) (Fig. 13). With regards to graft failure, there was large variability in the follow up period ranging from 1 year to 14 years. However among 489 recipients in 12 studies where two-year post pregnancy graft loss was reported, there were 32 cases of graft loss (9.2%). The change in preconception creatinine and post-pregnancy creatinine, was statistically significant $(1.23 \pm 0.16 \text{ mg/dl vs.} 1.37 \pm 0.27 \text{ mg/dl}, p = 0.007).$

Time of conception

Outcomes were also stratified by interval of < 2 years, 2-3 years, and > 3 years between pregnancy and kidney transplant (Table 2). Adverse pregnancy outcomes of

	Preclamn	sia among K	dnev Transn	lant Recipient		i Mean verall Value
Paper	Preclampsia, n	-		Preclampsia, %	95% C.I	Weight
Africa)' Donnell 1985 Random effects model leterogeneitynot applicable	4	38 38	-	10.526 10.526	[4.008; 24.898] [4.008; 24.898]	1.8 1.8
Asia ktrurk - 2015 J Durahimh 2008 Jfi A Y 2008 ezeshki 2004 Houssni 2016 trman Akar 2015 Sorgulu 2010 suella 2013 Iau 1994 Hooi 2003 (urata 2006	2 61 5 9 1 7 2 2 2 1 1 1 1 1 20	234 20 21 43 22 33 13 72		12.500 26.068 25.000 4.762 16.279 9.091 6.061 7.692 15.278 37.736	[3.145; 38.596] [20.845; 32.070] [10.806; 47.839] [25.320; 66.380] [0.667; 27.143] [7.964; 30.407] [2.284; 29.963] [1.521; 21.233] [1.072; 39.057] [8.667; 25.522] [25.804; 51.366]	1.1' 3.6' 2.1' 0.7' 2.3' 1.2' 1.2' 0.7' 2.7' 2.7'
Rahamimov 2006 'assaee 2007 'eon 2015 'ildirim 2005 'ou 2014 Isoon 2000 Random effects model leterogeneityt ² = 79%, τ ² = 0.4	11 45 55 6 11 7	69 95 119 20 41		15.942 47.368 46.218 30.000 26.829 14.583	[9.054; 26.542] [37.564; 57.380] [37.474; 55.202] [14.141; 52.724] [15.523; 42.252] [7.115; 27.566] [17.219; 30.493]	2.7' 3.3' 3.4' 2.5' 2.3' 36.4 !
Europe veia 2009	2	34	-	5.882	[1.476; 20.685]	1.2
Ilume 2013 candido 2016 bebska - Slizien 2014 bevresse 2017 sarcia 2005 serlei 2011 febral 2014 (ennedy 2012	14 5 1 6 5 6 16 6 6	53 22 57 19 27 61		26.415 9.434 4.545 10.526 26.316 22.222 26.230 20.690	[16.313; 39.799] [3.982; 20.739] [0.636; 26.145] [4.806; 21.515] [11.398; 49.787] [10.340; 41.448] [16.734; 38.614] [9.602; 39.049]	2.8' 2.0' 2.2' 1.8' 2.0' 2.9' 2.1'
tocha 2013 antos 2016 toumpos 2016 hompson 2003 an Buren 2012 entura 2000 ittle 2000	6 2 20 14 12 2 9	8 138 48 42 15		24,000 25,000 14,493 29,167 28,571 13,333 31,034	[11.200; 44.156] [6.304; 62.286] [9.544; 21.400] [18.098; 43.416] [16.998; 43.860] [3.355; 40.538] [17.006; 49.705]	2.0 1.0 3.1 2.7 2.6 1.1 2.3
opez 2011 Iarushak 1986 Random effects model leterogeneity/ ² = 40%, τ ² = 0.1	2	24	•	8.333 25.000	[2.093; 27.881] [11.686; 45.644] [16.145; 24.596]	1.2 2.0 35.7
Jorth America	3	11		27.273	[9.048; 58.566]	1.3
Criuz lemini 2007 Pahl 1993 Hadi 1986 Random effects model Reterogeneity/ ² = 60%, τ ² = 0.2			-	13.333 34.375 35.294 25.500	[7.327; 23.040] [20.163; 52.070] [16.786; 59.594] [14.518; 40.823]	2.6 2.5 1.9 8.2
Oceania evidiotis 2009 Random effects model eterogeneitynot applicable	156	577 577	:	27.036 27.036	[23.568; 30.809] [23.568; 30.809]	3.8 3.8
outh America	6		-	11.321	[5.176; 22.993]	2.2
Niveira 2007 rihuela 2016 ialdo 2005 ieitel 2004 ima 2016 Random effects mode / eterogeneity/ ² = 41%, t ² = 0.1		40 37 44		30.769 20.000 18.919 20.455 11.321 18.821	[19.784; 44.472] [10.330; 35.171] [9.296; 34.692] [11.001; 34.851] [5.176; 22.993] [13.403; 25.777]	2.8 2.3 2.2 2.4 2.2 14.2
Overall Effect leterogeneity/ ² = 68%, τ ² = 0.2	-	2676	0 20 40 60	21.539 80 100	[18.535; 24.881]	100.0

						Mean verall Value
	Cesarean Se	ction amo	ng Kidney Transpl	ant Recipients		
Paper	Cesarean Section, n L	ive Births, n		Cesarean Section, %	95% C.I	Weight
Africa D' Donnell 1985	8	22		36.364	[19.337; 57.665]	2.09
Rachdi 2013 Random effects model	16	16 38		100.000 77.533	[66.441; 99.819] [6.235; 99.445]	0.59 2.4 9
leterogeneity/ ² = 86%, τ ² = 7.097 \sia	8, χ ₁ = 7.29 (ρ < 0.01)					
sta ktrurk - 2015 I Duraihimh 2008	11 92	11 174		100.000 52.874	[57.544; 99.744] [45.448; 60.174]	0.59
A Durannin 2008 A Hassani 1995	92 12	31		38.710	[45.448, 60.174] [23.465; 56.542]	2.9
Alfi A Y 2008	6	20		30.000	[14.141; 52.724]	1.89
Celik 2011 Park 2001	13 16	23 25		56.522 64.000	[36.308; 74.777] [43.997; 80.091]	2.19 2.19
Pezeshki 2004	17	17		100.000	[43.337, 80.031]	0.59
El Houssni 2016	8	16		50.000	[27.290; 72.710]	1.89
Erman Akar 2015	24	29		82.759	[64.682; 92.636]	1.89
Guella 2013 Hooi 2003	10 18	21 49		47.619 36.735	[27.855; 68.158] [24.519; 50.930]	2.09 2.59
Rahbar 1997	10	45		100.000	[57.544; 99.744]	0.5%
Sabagh 1995	29	44	·	65.909	[50.897; 78.289]	2.49
Sharma 2009	19	58		32.759	[21.969; 45.741]	2.59
(u 2011 (assaee 2007	23 58	25 72		92.000 80.556	[73.056; 97.991] [69.799; 88.132]	1.29
(eon 2015	40	84		47.619	[37.204; 58.246]	2.79
/ildirim 2005	12	16		75.000	[49.176; 90.293]	1.69
/ou 2014 /loon 2000	16	30 26		53.333	[35.807; 70.074]	2.29
R andom effects model Heterogeneity/ ² = 78%, τ ² = 0.455	20	782		76.923 60.838	[57.240; 89.248] [51.874; 69.126]	1.99 37.6 9
Europe	ν, χ ₁₉ = 65.24 (β < 6.61)					
vreia 2009	19	27		70.370	[50.973; 84.436]	2.1
Arsan 1997	12	25		48.000	[29.637; 66.920]	2.1
Blume 2013 Brown 1991	24 8	32 23		75.000 34.783	[57.407; 86.975] [18.442; 55.711]	2.19
Candido 2016	20	41		48.780	[34.048; 63.728]	2.4
Debska - Slizien 2014	12	17		70.588	[45.815; 87.200]	1.79
Devresse 2017	28	43		65.116	[49.926; 77.752]	2.49
Farr 2014 Gerlei 2011	8 21	12 27		66.667 77.778	[37.588; 86.914] [58.552; 89.660]	1.59 1.99
Hebral 2014	38	57		66.667	[53.555; 77.623]	2.59
Kennedy 2012	9	23		39.130	[21.768; 59.762]	2.09
Queipo 2003	16	28		57.143	[38.680; 73.811]	2.29
Rieu 1997 Santos 2016	25 6	32 7		78.125 85.714	[60.703; 89.198] [41.940; 98.033]	2.09
Sarween 2016	246	390	-	63.077	[58.173; 67.725]	3.09
Sibanda 2007	110	153	: -	71.895	[64.263; 78.445]	2.89
Stoumpos 2016	80 19	102 32		78.431 59.375	[69.406; 85.356]	2.69
Thompson 2003 /an Buren 2012	19	41		39.024	[41.922; 74.743] [25.468; 54.518]	2.37
_ittle 2000	12	23		52.174	[32.495; 71.201]	2.19
_opez 2011	12	18	·	66.667	[42.878; 84.199]	1.89
Marushak 1986 Random effects model	18	24 1177	-	75.000	[54.356; 88.314] [57.677; 68.417]	1.99 46.5 9
$deterogeneity/^2 = 62\%, \tau^2 = 0.159$	17, $\chi^2_{21} = 55.42 \ (p < 0.01)$				[0	
North America Criuz Iemini 2007	52	64		81.250	[69.818; 89.032]	2.4
Pahl 1993	20	26		76.923	[57.240; 89.248]	1.99
Valtzer 1980	4	11		36.364	[14.331; 66.125]	1.59
Gill 2009 Random effects model Heterogeneity/ ² = 91%, τ ² = 1.055	127	294 395		43.197 61.761	[37.647; 48.924] [35.357; 82.667]	2.99 8.7 9
Oceania						
D' Connell 1989	4	10		40.000	[15.834; 70.260]	1.49
Nong 1995 Random effects model	10	11 21		90.909 69 474	[56.143; 98.736] [13.945; 96.967]	0.8 2.2
Heterogeneity/ 2 = 79%, τ^2 = 2.908	4. $\chi_1^2 = 4.84 \ (p = 0.03)$	21		05.4/4	[10.340, 90.907]	2.2
South America Drihuela 2016	28	29	_	96.552	[79.209; 99.516]	0.8
Saber 1995 Random effects model	16	21 50		76.190	[53.966; 89.728] [49.318; 98.473]	1.8 2.6
$\text{leterogeneity}^2 = 72\%, \tau^2 = 1.703$	3, $\chi_1^* = 3.62 \ (p = 0.06)$					
Οverall Effect leterogeneity/ ² = 78%, τ ² = 0.363	18, $\chi^2_{51} = 228.07 \ (p < 0.01)$	2463			[57.641; 67.289]	100.0
			0 20 40 60 80 10 Cesarean Section, %	0		

						Mean verall Value
	Gestational Dia	abetes amor	ng Kidney Tra	ansplant Recipients	;	
Paper	Gestational Diabetes, n	Pregnancies, n		Gestational Diabetes, %	95% C.I	Weights
Africa Ghanem 2005 <i>Random effects mode</i> Heterogeneitynot applicable	4 21	67 67	+	5.970 5.970	[2.259; 14.852] [2.259; 14.852]	6.3% 6.3%
Asia Aktrurk - 2015 Alfi A Y 2008 Celik 2011 Guella 2013 Hau 1994 Sabagh 1995 Yildirim 2005 You 2014 Random effects mode Heterogeneity ² = 4%, τ ² = 0.0		20 31 33 13 52 20		6.250 0.000 3.226 0.000 0.000 13.462 5.000 2.439 6.797	[0.873; 33,541] [0.147; 28,738] [0.453; 19,642] [0.091; 19,588] [0.220; 38,387] [6.555; 25,647] [0.700; 28,220] [0.343; 15,387] [3.782; 11.917]	3.4% 2.1% 2.1% 2.1% 7.1% 3.4% 3.4% 27.0%
Europe Areia 2009 Candido 2016 Devresse 2017 Farr 2014 Hebral 2014 Kennedy 2012 Rocha 2013 Sarween 2016 Thompson 2003 Lopez 2011 Random effects mode Heterogeneity/ ² = 53%, t ² = 0.		53 57 12 61 29 25 569 48		8.824 1.887 1.754 - 16.667 21.311 6.897 8.000 12.830 2.083 4.167 8.968	[2.874; 24.043] [0.265; 12.212] [0.247; 11.426] [4.198; 47.720] [1.731; 23.751] [2.009; 26.944] [10.323; 15.837] [0.293; 13.361] [0.584; 24.354] [5.551; 14.172]	5.7% 3.4% 3.5% 4.6% 4.8% 4.8% 3.4% 3.4% 50.0%
North America Pahl 1993 Random effects mode Heterogeneitynot applicable	e l 1	32 32	-	3.125 3.125	[0.438; 19.113] [0.438; 19.113]	3.4% 3.4 %
Oceania Levidiotis 2009 Random effects mode Heterogeneitynot applicable	e l 6	577 577		1.040 1.040	[0.468; 2.295] [0.468; 2.295]	7.0% 7.0%
South America Oliveira 2007 Random effects mode Heterogeneitynot applicable	el 4	52 52	*	7.692 7.692	[2.917; 18.772] [2.917; 18.772]	6.2% 6.2 %
Overall Effect Heterogeneity/ ² = 69%, τ ² = 0.	6513. $\chi^2_{21} = 68.69 \ (p < 0.01)$	1866	0 20 40	5.733 60 80 100 I Diabetes, %	[3.661; 8.871]	100.0%

induced abortion rates and neonatal deaths were highest in the 2–3 year interval following kidney transplant as compared to <2 year interval and >3 year interval (16% vs. 11% vs. 10, and 9% vs. 3% vs. 4% respectively). Cesarean section rate and live birth rate were also less favorable in this interval of 2–3 years than > 3 year, and <2 year interval (68% vs. 75% vs. 74, and 73% vs. 65% vs. 42% respectively). Maternal complication of preeclampsia was higher in the 2–3 interval, and > 3 year interval than <2 year interval (24% vs. 23% vs. 13%). Spontaneous abortion rates were highest in >3 year interval followed by 2–3 interval, and <2 interval (16% vs. 14% vs. 10%).

Maternal age for conception

We further stratified the pregnancy, maternal, fetal, and graft outcomes by maternal age categories (Table 3).

Lower live birth rate was observed in women with maternal age 29–34 years than those < 29 years (74% vs. 76%). Rates of spontaneous abortion were highest in women < 25 years and > 35 years followed by women with maternal age 25–34 years (20% vs. 18% vs. 11%). Preeclampsia rates were higher in women with maternal age > 35 years (27%) and 29–34 years (26%) followed by < 25 years (17%) and 25–29 years (14%).

Discussion

The results of our meta-analysis show that although majority of pregnancies in women after kidney transplant result in live birth, both maternal and fetal adverse events are common. Rates of preeclampsia, still birth, and cesarean section were significantly higher than in the general population. In the cohort considered for the analysis, a quarter of women had serious pregnancy

Brogno	nov induced	Hyportopoio	n among Kidney 1	Francolant		verall Value
Flegha	•		U F	•	•	
Paper	Hypertension, n	Pregnancies, n	H	lypertension, %	95% C.I	Weights
Africa O' Donnell 1985 Ghanem 2005 Random effects mode Heterogeneityl ² = 27%, τ^2 = 0.			ŧ	10.526 19.403 16.062	[4.008; 24.898] [11.614; 30.608] [9.042; 26.921]	2.3% 2.6% 4.9%
Asia Alfi A Y 2008 Celik 2011 Pezeski 2004 El Houssni 2016 Gorgulu 2010 Guella 2013 Hau 1994 Hooi 2003 Rahamimov 2006 Rahbar 1997 Rizvi 2009 Sabagh 1995 Sharma 2009 Tan 2002 Xu 2011 Yassaee 2007 Yildirim 2005 Yoshikawa 2016 Moon 2000 Random effects mode Heterogeneity ² = 87%, t ² = 1.		31 20 21 22 33 13 72 69 14 72 52 82 82 82 82 82 82 82 82 82 82 95 20 65	$\begin{bmatrix} 1 \\ + \\ + \\ + \\ + \\ + \\ + \\ + \\ + \\ + \\$	0.000 12.903 20.000 9.524 36.364 15.152 0.000 8.333 24.638 28.571 80.556 28.846 10.976 4.762 36.842 35.789 15.000 52.308 8.333 21.012	[0.147; 28,738] [4.928; 29,745] [7,713; 42,785] [2.393; 31.125] [19.337; 57.665] [6.450; 31.622] [0.220; 38.387] [3.792; 17.334] [15.901; 36.113] [11.147; 56.051] [69,799; 88.132] [18.201; 42.484] [5.810; 19.4; 17.142] [23.181; 53.000] [26.816; 45.883] [4.917; 37.584] [40.267; 64.086] [3.163; 20.192] [13.576; 31.056]	1.1% 2.3% 2.0% 2.4% 1.1% 2.5% 2.7% 2.6% 2.6% 2.6% 2.6% 2.6% 2.6% 2.6% 2.6
Europe Areia 2009 Arsan 1997 Brown 1991 Candido 2016 Debska - Slizien 2014 Devresse 2017 Farr 2014 Kennedy 2012 Kuvacic 2000 Pietrzak 2013 Rieu 1997 Sibanda 2007 Stoumpos 2016 Talaat 1994 Thompson 2003 Random effects mode Heterogeneityl ² = 92%, t ² = 1.	2 2 7 7 2 0 1 1 3 3 10 15 10 7 3 1 10 7 3 1 10 7 3 1 10 7 7 10 10 7 10 10 10 10 10 10 10 10 10 10 10 10 10	33 27 53 22 57 12 29 23 40 33 40 33 193 138 25		11.765 6.061 14.815 13.208 31.818 3.509 0.000 48.276 56.522 85.000 48.485 7.772 7.246 28.000 64.583 23.551	[4.487; 27.456] [1.521; 21.233] [5.673; 33.461] [6.429; 25.208] [15.986; 53.370] [0.879; 12.973] [0.236; 40.319] [31.060; 65.911] [36.308; 74.777] [70.406; 93.102] [32.228; 65.069] [4.739; 12.490] [3.943; 12.944] [13.973; 48.215] [50.232; 76.715] [12.610; 39.673]	2.3% 2.0% 2.5% 2.0% 1.1% 2.5% 2.6% 2.6% 2.6% 2.6% 2.6% 2.4% 35.0%
North America Criuz lemini 2007 Hadi 1986 Waltzer 1980 Muirhead 1992 Random effects mode Heterogeneityr ² = 38%, t ² = 0.		17 15		29.333 41.176 13.333 45.455 33.185	[20.160; 40.560] [21.039; 64.776] [3.355; 40.538] [26.473; 65.856] [22.475; 45.973]	2.7% 2.4% 1.9% 2.5% 9.5%
South America Ribeiro 2013 Saber 1995 Lima 2016 Random effects mode Heterogeneityi ² = 93%, s ² = 1.		25	+	67.742 68.000 15.094 47.952	[49.722; 81.682] [47.837; 83.119] [7.733; 27.385] [15.061; 82.720]	2.5% 2.5% 2.5% 7.5%
Overall Effect Heterogeneity/ ² = 88%, τ ² = 1.		1939	0 20 40 60 80 1 Pregnancy induced Hypertension	1 00 1, %	[18.118; 31.471]	100.0%

Fig. 10 Forest Plot showing outcome of pregnancy induced hypertension among kidney transplant recipients overall, and across different geographical regions

complications, defined as at least one of preterm delivery, first or second trimester loss, stillbirth, or neonatal death. Additionally, rates of preterm delivery, still births, and neonatal mortality were higher as compared with the US recent national data. The live birth rates in women after kidney transplant were higher than in the general population (73% vs. 62%) and this trend was consistent throughout the globe [10]. Our study confirms the findings from The National Transplant Pregnancy Registry from the United States

					• 0	Mean verall Valu
		-	idney Transp	lant Recipients		
aper	Pre-term Birth, n Live	Births, n		Pre-term Birth, %	95% C.I	Weigh
f rica Donnell 1985	11	22		50.000	[30.243; 69.757]	2.0
achdi 2013	5	16	· · · · · · · · · · · · · · · · · · ·	31.250	[13.639; 56.677]	1.6
andom effects model eterogeneity/ $\hat{\tau}$ = 24%, τ^2 = 0.07	45, $\chi_{4}^{2} = 1.32 \ (p = 0.25)$	38			25.242; 60.722]	3.7
sia						
trurk - 2015	4	11		36.364	[14.331; 66.125]	1.4
Duraihimh 2008	71	174	-	40.805	[33.752; 48.258]	3.2
fi A Y 2008	6	20		30.000	[14.141; 52.724]	1.8
elik 2011	5	23		21.739	[9.349; 42.797]	1.7
eyatani 2012	5	17		29.412	[12.800; 54.185]	1.6
ırk 2001 Houssni 2016	12 3	25 16		48.000 18.750	[29.637; 66.920] [6.170; 44.746]	2.1 1.3
man Akar 2015	7	29		24.138	[11.966; 42.688]	2.0
au 1994	2	7	· · · · · · · · · · · · · · · · · · ·	28.571	[7.202; 67.338]	0.9
poi 2003	17	49	·	34.694	[22.780; 48.893]	2.6
hamimov 2006	33	55	·	60.000	[46.655; 72.009]	2.7
hbar 1997	7	11	· · · · · · · · · · · · · · · · · · ·	- 63.636	[33.875; 85.669]	1.4
bagh 1995	30	44	: —	68.182	[53.190; 80.163]	2.5
2011	7	25		28.000	[13.973; 48.215]	2.0
ssaee 2007	16	72		22.222	[14.084; 33.244]	2.
on 2015 dirim 2005	27	84		32.143	[23.057; 42.817]	2.9
dirim 2005 u 2014	5	16		31.250	[13.639; 56.677]	1.6
ou 2014 Don 2000	6 12	30 26		20.000 46.154	[9.272; 37.949] [28.390; 64.951]	1.9 2.2
andom effects model		734	-		[29.631; 43.208]	38.6
terogeneity/ ² = 66%, τ ² = 0.24	92, χ ₁₈ = 52.98 (β < 0.01)					
urope eia 2009	16	27		59.259	[40.300; 75.811]	2.2
ume 2013	19	32	· · · · · · · · · · · · · · · · · · ·	59.375	[41.922; 74.743]	2.3
own 1991	13	23	_	56.522	[36.308; 74.777]	2.1
andido 2016	16	41		39.024	[25.468; 54.518]	2.5
ebska - Slizien 2014	4	17		23.529	[9.118; 48.550]	1.5
evresse 2017	28	43		65.116	[49.926; 77.752]	2.5
arr 2014	6	12		50.000	[24.387; 75.613]	1.5
ebral 2014	24	57		42.105	[30.064; 55.165]	2.7
ennedy 2012	8	23		34.783	[18.442; 55.711]	2.0
uvacic 2000	3 16	15 28		20.000	[6.590; 46.975]	1.3
ueipo 2003 ieu 1997	14	32		57.143 43.750	[38.680; 73.811] [27.894; 60.995]	2.2 2.3
antos 2016	3	7		43.750	[14.373; 77.017]	2.3
banda 2007	77	153		50.327	[42.462; 58.176]	3.2
oumpos 2016	62	102		60.784	[51.019; 69.757]	3.0
10mpson 2003	18	32	_	56.250	[39.005; 72.106]	2.3
an Buren 2012	17	41		41.463	[27.565; 56.868]	2.5
ttle 2000	17	23		- 73.913	[52.766; 87.784]	1.8
arushak 1986	8	24		33.333	[17.627; 53.881]	2.0
andom effects model terogeneity/ ² = 49%, τ ² = 0.11	07, $\chi^2_{18} = 35.34 (p < 0.01)$	732	-	49.475	[43.839; 55.125]	41.2
orth America	-					
pro 2002	15	32	: — • —	46.875	[30.588; 63.857]	2.3
1 2009	82	294	: -	27.891	[23.063; 33.293]	3.3
andom effects model terogeneity/ ² = 79%, τ ² = 0.26	89, $\gamma_{s}^{2} = 4.78 \ (p = 0.03)$	326		35.358	[19.763; 54.847]	5.7
ceania						
ong 1995	3	11	· · · · · · · · · · · · · · · · · · ·	27.273	[9.048; 58.566]	1.3
/ld 2013	284	526	+	53.992	[49.714; 58.212]	3.4
andom effects model terogeneity ^β = 64%, τ ² = 0.41		537			[22.067; 69.762]	4.7
outh America	18	29	_ _	62.069	[43.595; 77.601]	2.2
eitel 2004	10	27		37.037	[21.220; 56.229]	2.2
iber 1995	14	21		66.667	[44.667; 83.208]	1.9
andom effects model terogeneity/ 2 = 61%, τ^2 = 0.26	24. $\gamma_{a}^{2} = 5.07 \ (p = 0.08)$	77		55.038	36.749; 72.060]	6.3
	- mg	2444		13 444	38 705. 47 6351	100 /
νerall Effect terogeneity/ ² = 73%, τ ² = 0.24	44, χ _e ² = 170.91 (p < 0.01)	2444	· · · · · · · · · · · · · · · · · · ·	43.114 [[38.705; 47.635]	100.0
			0 20 40 60 80	100		
			Pre-term Birth, %			

	Neonatarin	iontanty amo	ig inally fram	splant Recipients		
aper	Neonatal Mortality, n	Pregnancies, n		Neonatal Mortality, %	95% C.I	Weight
frica Donnell 1985 andom effects mode eterogeneitynot applicable		7 38 38	-	18.421 18.421	[9.044; 33.897] [9.044; 33.897]	12.0 12.0
sia						
drurk - 2015				6.250	[0.873; 33.541]	2.4
Duraihimh 2008	-	7 234	i	2.991	[1.433; 6.140]	13.7
ezeshki 2004	2	2 20		10.000	[2.513; 32.380]	4.5
Houssni 2016		0 21	÷	0.000	[0.141; 27.741]	1.3
orgulu 2010	(0 22		0.000	[0.135; 26.811]	1.3
ooi 2003		1 72		1.389	[0.195; 9.204]	2.5
urata 2006		53		0.000	[0.058; 13.146]	1.3
harma 2009		2 82	-	2.439	[0.611; 9.231]	4.8
assaee 2007		3 95	•	3.158	[1.022; 9.336]	6.9
Idirim 2005		1 20		5.000	[0.700; 28.220]	2.5
ou 2014		0 41		0.000	[0.074; 16.378]	1.3
andom effects mode		676	1. I I I I I I I I I I I I I I I I I I I		[2.036; 4.940]	42.5
$terogeneity/^2 = 0\%$, $\tau^2 = 0$,		070		3.762	[2.030, 4.940]	42.5
urope						
ume 2013		1 53		1.887	[0.265; 12.212]	2.5
andido 2016	1	2 53		3.774	[0.946; 13.873]	4.8
arr 2014	(0 12	÷	0.000	[0.236; 40.319]	1.3
erlei 2011	(0 27	÷	0.000	[0.111; 22.962]	1.3
ebral 2014	(0 61	*	0.000	[0.050: 11.618]	1.3
ennedy 2012	-	1 29		3.448	[0.484; 20.791]	2.5
uvacic 2000	(0 23		0.000	[0.129; 25.942]	1.3
ocha 2013	(0 25	÷	0.000	[0.119; 24.361]	1.3
toumpos 2016		2 138	+	1.449	[0.363; 5.607]	4.9
urgiss 1991		1 22	i	4.545	[0.636; 26.145]	2.5
nompson 2003		2 48	· · · · · · · · · · · · · · · · · · ·	4.167	[1.044; 15.190]	4.7
ttle 2000		2 29		6.897	[1.731; 23.751]	4.6
arushak 1986		0 24		0.000		1.3
andom effects mode	-	544	•		[1.775; 4.988]	34.2
$terogeneity/^2 = 0\%$, $\tau^2 = 0$,	(₁₂ = 4.57 (p = 0.97)					
orth America iuz lemini 2007	(0 75	÷	0.000	[0.041; 9.654]	1.3
adi 1986		0 17	÷	0.000	[0.172; 32.208]	1.3
andom effects mode eterogeneity/ ² = 0%, τ ² = 0,		92	T	1.346	[0.189; 8.971]	2.6
ceania						
Connell 1989		1 18		5.556	[0.777; 30.652]	2.4
andom effects mode		18			[0.777; 30.652]	2.4
terogeneitynot applicable		10		0.000		
outh America						
istelli 2016		0 53	÷	0.000	[0.058; 13.146]	1.3
ihuela 2016		1 40	÷	2.500	[0.351; 15.728]	2.5
aber 1995		. 20		4.000	[0.561; 23.547]	2.5
andom effects mode terogeneity/ ² = 0%, τ ² = 0, τ		118		2.466	[0.714; 8.164]	6.3
verall Effect		1486		3.792	[2.775; 5.161]	100.0
$terogeneity/^2 = 6\%$. $\tau^2 = 0.0$	506, $\chi^2_{30} = 31.97 \ (p = 0.37)$		r i i	· · · · · · · · · · · · · · · · · · ·	[, ee.ı]	

that reported a live birth rate of 71–76% [7]. Similarly, meta-analysis done by Deshpande et al. examined pregnancy outcomes of 4706 pregnancies in women with kidney transplant and reported a live birth rate of 73.5% [9]. The higher live birth rate, although appears encouraging, may reflect a reporting bias or a selection bias in which relatively healthy women decided to pursue pregnancy, and subsequently received better medical support by multiple specialties. It is also important to consider that there are inconsistencies in definition of live birth rate used in various studies, for example live birth rate was defined as per 1000 female transplant recipients in some studies, whereas per 1000 pregnancies in transplant recipients in others [7, 20]. Live birth rate in general population (comparison group) is defined by Centers for Disease Control as live births per 1000 population [10]. Additionally, it remains unclear how the multiple gestation pregnancy outcomes were evaluated in these studies. Contrary to the above findings of successful pregnancies, a US health utilization study found a much lower live birth rate of 55% in kidney transplant recipients. They attributed this finding of low live birth rate to underestimation of fetal loss [20]. Davison et al. estimated that just under 40% of conceptions do not go

						Mean verall Valu
Acu	te Rejection	s among	Kidney Trar	nsplant Recipients	;	
Paper Acute R	ejection, n Rece	pients, n		Acute Rejection, %	95% C.I	Weigh
frica						
b' Donnell 1985 Random effects model eterogeneitynot applicable	1	21 21	-	4.762 4.762 [[0.667; 27.143] [0.667; 27.143]	2.8 2.8
sia						
drurk - 2015	1	12	-	8.333	[1.160; 41.319]	2.
Duraihimh 2008	7	140	-	5.000	[2.402; 10.116]	6
A Y 2008	1	12		8.333	[1.160; 41.319]	2
Houssni 2016	2	12		16.667	[4.198; 47.720]	3
man Akar 2015	5	43		11.628	[4.924; 25.054]	5
u 1994	1	11		9.091	[1.264; 43.857]	2
ur 2005	23	60		38.333	[26.976; 51.125]	6
hbar 1997 arma 2009	1 10	13 42		7.692 23.810	[1.072; 39.057]	2
ssaee 2007	2	42 74		23.810	[13.317; 38.863] [0.677; 10.170]	4
u 2014	2	29		6.897	[1.731; 23.751]	4
andom effects model	2	448	- <u>-</u>		5.681; 20.382]	47.
terogeneity/ $\hat{\tau}$ = 77%, τ^{2} = 1.0024, χ^{2}_{10} = 44.	09 (p < 0.01)	440		11.040 [0.001, 20.002	47.
urope						
eia 2009	2	28	-	7.143	[1.793; 24.477]	4
ime 2013	2	34		5.882	[1.476; 20.685]	4
indido 2016	3	36		8.333	[2.713; 22.864]	4
nnedy 2012	1	18		5.556	[0.777; 30.652]	2
vacic 2000	2	15	-	13.333	[3.355; 40.538]	3
laat 1994	1	19		5.263	[0.736; 29.386]	2
ntura 2000	1 1	15		6.667	[0.931; 35.199]	2
lle 2000	1	19		5.263	[0.736; 29.386]	2
terogeneity/ $\hat{\tau} = 0\%$, $\hat{\tau} = 0$, $\hat{\chi}_7 = 1.28$ (p = 0	99)	184	Ť	7.328 [4.297; 12.223]	27.
orth America						_
iuz lemini 2007	4	60	-	6.667	[2.525; 16.456]	5
andom effects model erogeneitynot applicable		60	T.	0.007 [2.525; 16.456]	5.
ceania						
Connell 1989	1	11		9.091	[1.264; 43.857]	2
erogeneitynot applicable		11		9.091 [1.264; 43.857]	2.
outh America	_					
huela 2016	2 7	32		6.250	[1.568; 21.811]	4
Ido 2005		30		23.333	[11.551; 41.495]	5.
na 2016	2	36		5.556	[1.394; 19.669]	4.
andom effects model terogeneity/ = 64%, τ ² = 0.6820, χ ₂ ² = 5.55	6 (p = 0.08)	98		10.713 [3.586; 27.907]	13.
verall Effect		822	-	9.407 [6.369; 13.683]	100.
terogeneity/ ² = 62%, τ^2 = 0.6174, χ^2_{24} = 62.	76 (p < 0.01)		0 20 40 60			
			Acute Rejection	ns, %		

beyond the first trimester, but of those that do, greater than 90% end successfully [21]. Another explanation of high live birth rate in our study could be the exclusion of studies that reported pregnancy outcomes with teratogenic immunosuppressive medications of mycophenolate and sirolimus.

Our study highlights the significantly higher risk of maternal and fetal complications in women with kidney transplants. About a quarter of women developed preeclampsia, and the rates of preeclampsia were almost six fold higher as compared to the general US population (21.5% vs. 3.8%) [16]. Vannevel et al. in an international multicenter retrospective cohort of 52 women who underwent kidney transplantation reported preeclampsia rate of as high as 38%, and chronic hypertension rate of 27% [22]. Hypertension is common in kidney transplant recipients prior to conception with a reported incidence of 52 to 69% [1]. Several factors can contribute to the onset of hypertension after renal transplantation, including but not limited to the type of immunosuppressive therapy (calcineurin inhibitors and corticosteroids), allograft function, donor type, obesity, alcohol, smoking, and presence of a native kidney (increased production of renin) [23]. Diagnosis of superimposed preeclampsia can be difficult in kidney transplant patients due to higher frequency of pre-existing hypertension and proteinuria [1, 24].

We found significant differences in rates of gestational diabetes mellitus between various geographical location,

	< 2 years	> 2-3 years	> 3 years
Number of papers	4	15	44
Number of pregnancies	149	835	3182
Mean maternal age (year)	28.3	29.4	29.1
Pregnancy Outcomes			
Live birth	73.8%	68.3%	75.4%
Induced abortion	10.7%	16.1%	10.2%
Spontaneous abortion	10.3%	14.0%	16.3%
Still birth	6.7%	5.1%	3.7%
Neonatal deaths	3.4%	9.3%	3.7%
Cesarean section	41.8%	72.7%	64.5%
Maternal Outcomes			
Preeclampsia	13.2%	24.3%	22.8%
Pregnancy induced hypertension	12.1%	30.8%	23.0%
Gestational diabetes	0.0%	8.8%	7.2%
Fetal Outcomes			
Pre-term delivery	41.9%	41.6%	45.4%
Mean gestation time (weeks)	36.1	34.5	34.9
Birth weight (grams)	2349.00	2533.21	2460.79
Graft Outcomes			
Acute rejection	8.1%	5.1%	3.0%
Graft loss	16.7%	14.6%	6.3%

Table 2 Pregnancy-related outcomes stratified by study meaninterval between transplant and pregnancy

Table 3 Pregnancy-related	outcomes	stratified	by	study	mean
maternal age					

Study mean maternal age (years)				
	< 25	25–29	30-34	≥35
Number of papers	3	22	35	1
Number of pregnancies	103	723	3474	11
Mean maternal age (year)	23.3	27.4	30.2	36.0
Pregnancy Outcomes				
Live birth	75.8%	75.8%	73.9%	na
Induced abortion	14.0%	11.3%	11.0%	na
Spontaneous abortion	19.8%	16.0%	13.3%	18.2%
Still birth	2.9%	5.3%	3.6%	9.1%
Neonatal deaths	na	5.4%	3.0%	na
Cesarean section	48.0%	68.3%	63.6%	na
Maternal Outcomes				
Preeclampsia	17.1%	13.7%	26.5%	27.3%
Pregnancy induced hypertension	16.5%	25.2%	23.4%	na
Gestational diabetes	na	5.8%	7.0%	na
Fetal Outcomes				
Pre-term delivery	na	46.4%	47.4%	na
Mean gestation time (weeks)	35.5	35.5	34.6	na
Birth weight (grams)	2460.0	2607.7	2456.9	na
Graft Outcomes				
Acute rejection	3.8%	3.3%	5.8%	na
Graft loss	na	12.1%	10.4%	27.3%
*na not available				

for example rates were as high as 8.9% in Europe and as low as 1% in Oceania. Although, the increased rate of gestational diabetes in kidney transplant patients can be well explained by the use of immunosuppressive medications like steroids and calcineurin inhibitors, the striking differences between rates of gestational diabetes according to geographic location also highlights the importance of predisposition to diabetes due to ethnicity. Unfortunately, it was not possible to evaluate the differences in immunosuppressive medications as usually they are individualized to the needs of the patients and transplant center protocol [1, 25].

Rates of stillbirth and neonatal mortality were significantly higher in our study as compared to the general population. While prior studies have not reported higher rates of neonatal mortality and stillbirths in kidney transplant recipients, the current study finding is highly significant. Possible reasons could be prematurity, preeclampsia or presence of other risk factors like hypertension, proteinuria, and serum creatinine of 1.5 mg/dl or higher [26–28]. While it was not possible to determine the exact cause for stillbirth or neonatal mortality, this study finding is critical for counselling of women of child bearing age contemplating pregnancy. In our study, the rate of cesarean section was higher than two folds as *na not available

compared to general population in United States, and varied from 60 to 77% across different geographical locations. Bramham et al. reported that more than three quarters of the deliveries in kidney transplant recipients were by cesarean section, but only 3% were performed for the indication of renal transplant [3]. Vaginal delivery should not be impaired in kidney transplant patients, as the pelvic allograft does not obstruct the birth canal in most patients [1]. This exceptionally higher rates of cesarean sections in kidney transplant recipients can be attributed to fetal and maternal complications, but warrants further study. There was a high rate of premature births in the transplant population in the present study and close to half of the live births were premature deliveries. Prior studies have showed a preterm birth rate of 40-60% in kidney transplant recipients [9, 29]. Fetal complications, suspected renal compromise or preeclampsia are some of the common indications of early iatrogenic delivery. Interestingly, only quarter of preterm deliveries in renal transplant recipients are induced [3, 7].

The optimal time to conception after renal transplant continues to remain an area of contention. The ideal

time of conception in women with renal transplant is between 1 and 2 years after transplantation according to guidelines by American Society of Transplantation, whereas European best practice guidelines recommend delaying pregnancy for a period of 2 years after transplantation [30, 31]. In our study, live birth rate was lowest and neonatal deaths were highest in the 2-3 year interval following kidney transplant. Maternal complication of cesarean section and preeclampsia were higher in the 2-3 and > 3 year interval. In contrast, Deshpande et al. reported both the highest maternal complications of preeclampsia, cesarean section, and gestational diabetes, and least favorable delivery outcome of preterm births in the < 2 year interval as compared to > 2 year interval between kidney transplant and pregnancy [9]. However their analysis was limited by inclusion of only 3 studies in the < 2 interval following kidney transplant. Overall, fetal outcomes in < 2 year interval seem most favorable in our study but merits further investigation due to limitation of the retrospective study design, small numbers, and possible reporting bias associated with data from voluntary registries.

A significant strength of our study is that it involves a large number of pregnant renal transplant recepients from all around the globe, thus providing us with information about pregnancy outcomes for a heterogenous population. Additionally, we have analyzed region specific outcomes and identified outcomes which may require intensive management pertaining to that region. This will help in making future region specific guidelines for follow up and management of pregnancy in kidney transplant recpients. The following limitations should be considered when interpreting the findings of our study. We examined pregnancy outcomes over several decades in the present study. While it is expected for the outcomes to change due to improvement in obstetric care in kidney transplant recipients over the course of time, subgroup analysis for studies from 2000 to 2017 showed consistent results. There were inconsistencies in the definition of live birth rate amongst different studies that may have affected the results. Reporting bias may have affected the miscarriage rate. We were unable to account for differences in socioeconomics, and healthcare conditions among the different geographic regions. Due to lack of individual patient data, we were not able to assess pregnancy outcomes in relation to immunosuppression regimens.

Conclusions

This meta analysis of pregnancy outcomes in 6712 pregnancies in 4174 kidney transplant recipients with data spread over different decades from all over the world shows favorable outcomes with live birth rates exceeding that in the recent national population. Majority of patients preserve their graft. However,

pregnancy after renal transplant confers significant risk in terms of maternal and fetal adverse events, including increased rates of preeclampsia, gestational diabetes, cesarean section rates, and pregnancy induced hypertension. The risk of prematurity and low birth rate are also high. Areas which need to be studied in the future include type of immunosuppression and its correlation with specific pregnancy outcomes; and evaluation of risk factors associated with specific maternal and fetal adverse events. The definitions used in evaluating these outcomes also need to be standardized. The results of this study can help the health care providers with appropriate counseling and individualized management of this high risk population.

Additional files

Additional file 1: Reproducible search strategy. (DOCX 149 kb) Additional file 2: Subgroup analysis of various pregnancy outcomes in kidney transplant recipients for studies published from 2000 to 2017. (DOCX 16 kb)

Abbreviations

CI: Confidence interval; US: United States

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None.

Author contributions

SS initiated the study, designed the study and wrote the initial manuscript. RV, Ayank Gupta, RJ and MS contributed to the study design, and study figures, analyzed and interpreted the data, and did the manuscript review. JW contributed to the sudy design, data analysis, interpretation of data, and manuscript review. EK contibuted to literature search, and manuscript review. TK contributed in study design and manuscript review. Anu Gupta contributed in manuscript writing and manuscript review. TG contributed to the study design, implementation of the study, study figures, and manuscript review. PV assisted SS with study design and implementation, revision of the manuscript and did the final approval of the manuscript. All authors reviewed the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All the authors have no disclosures and competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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