Diabetic kidney disease and pregnancy outcomes: a systematic review

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Abstract

Introduction: We systematically reviewed all relevant literature on diabetic kidney disease (DKD) and pregnancy published in the last 20 years to provide accurate and up-to-date information to inform family planning and maternal care.

Methods: A systematic review was completed in PubMed and Embase. Papers reporting maternal, fetal or renal outcomes of pregnant women with DKD published between 2001 and 2020 were included.

Results: 799 potentially relevant articles were identified, 731 of which were excluded on abstract alone. 68 full-text articles were reviewed and 15 papers were included as they met the selection criteria but were heterogeneous for size, study setting and years studied. The definition of DKD varied between papers and changed over time. 843 women with 873 pregnancies were included. There were high rates of pre-eclampsia and caesarean section, up to 64% and 100% respectively. Prematurity and neonatal intensive care admission were common, reported in up to 100% and 75%, respectively. Maternal and fetal complications were more common with more severe proteinuria and renal impairment. Pregnancy did not hasten progression of DKD.

Discussion: Adverse pregnancy outcomes are frequently encountered and correlate with degree of proteinuria and renal impairment. This information enables individualised risk stratification when a woman is considering pregnancy.

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Key words: diabetes mellitus, pregnancy, diabetic nephropathy, diabetic kidney disease

Introduction

Pre-existing diabetes is common, affecting one in every 250 pregnancies,[1] with diabetic kidney disease (DKD) affecting 2–8% of those.[2] Women with diabetes have poorer pregnancy outcomes compared with healthy women;[1,3] historically, those with DKD have had even worse outcomes, with fetal mortality rates up to 60%.[4] More recently, with advances in diabetes management, obstetric and neonatal care, these outcomes have improved, with fetal survival of 95–99%.[5,6]

Given this relatively high incidence of DKD and the rising prevalence of diabetes,[7] it is critical to have information on DKD in pregnancy. However, our knowledge of DKD and pregnancy is limited. Much of our information comes from case series and single-centre observational studies, often including small numbers of women, spanning many years. The definition of DKD has also evolved, with earlier studies only concerned with macroalbuminuria and more recent studies including microalbuminuria.[5,8]

We reviewed all relevant literature on DKD and pregnancy published in the last 20 years reporting on maternal, fetal and longer term renal outcomes. This systematic review in a modern timeframe aims to give women considering or entering pregnancy and their healthcare professionals the available information on renal, maternal and fetal risks, to allow them to make informed decisions when family planning and improve care during and after pregnancy.

Methods

This systematic review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[9]

Search strategy

We conducted electronic literature searches in PubMed and Embase. The initial search was carried out in August 2020 and repeated in October 2020.The databases were searched for 'diabetic nephropathy', 'diabetic kidney disease', 'microalbuminuria' AND 'pregnancy'. The search was deliberately broad to increase sensitivity. The reference lists of selected papers were searched for references missed by our search strategy.

Selection criteria

Papers reporting maternal, fetal and/or renal outcomes of pregnant women with DKD published between 2001 and 2020 were included. To reduce publication bias, case reports and series including ≤5 women were excluded. Other exclusion criteria included conference abstracts, papers in languages other than English and pregnancies in women with kidney transplants. If participants were included in more than one report, the larger study was included.

The search was completed in duplicate by SG and SS. They completed the searches independently and matched results. Titles and abstracts were screened by SG and SS. Full texts were assessed by SG. Discrepancies were resolved by discussion.

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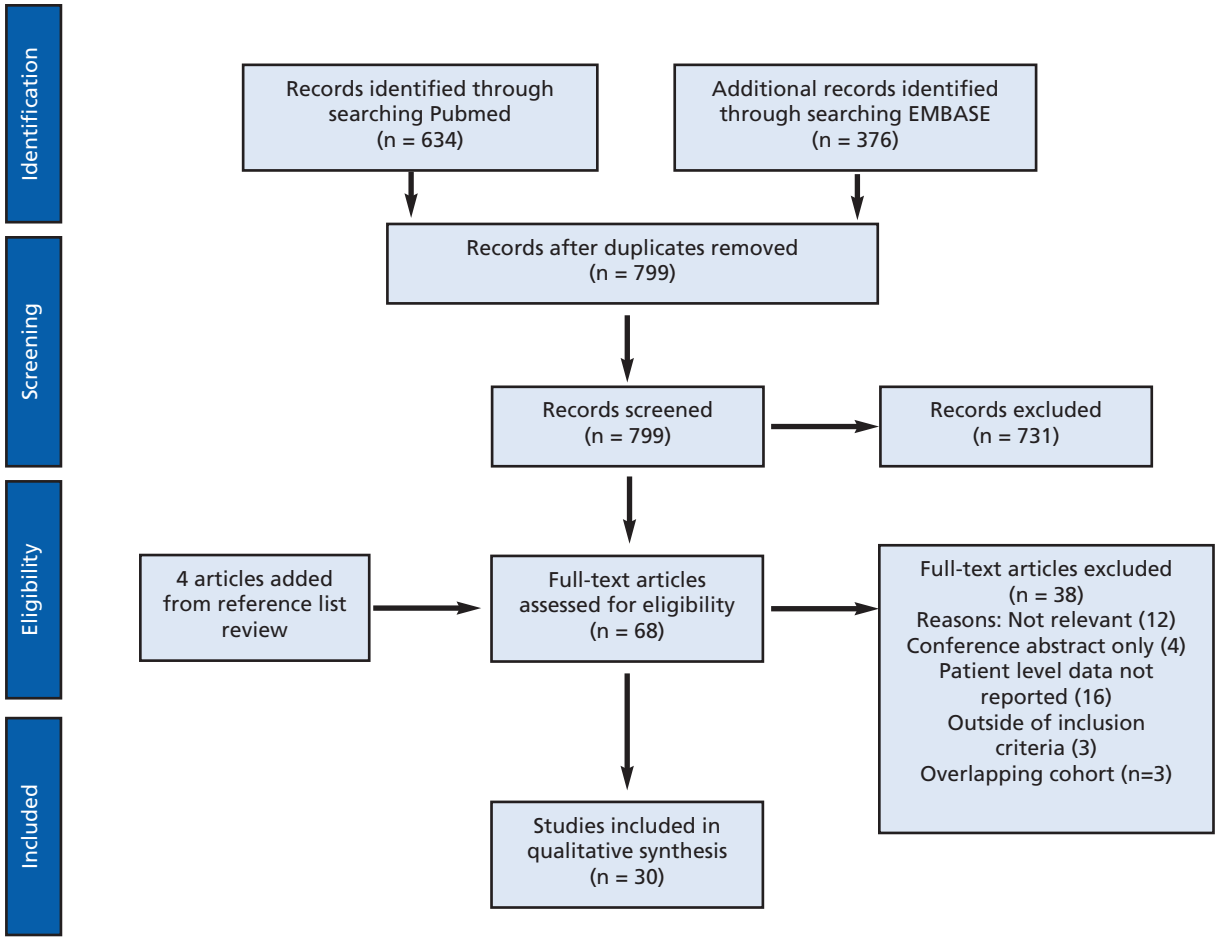
Figure 1. Study selection



Data collection and analysis

The data were analysed according to PICOS criteria as follows. The patients (P) were women with DKD. The intervention (I) was considered to be pregnancy, in the absence of an actual therapeutic intervention. The control (C) groups included healthy or women without DKD who were pregnant or women with DKD without pregnancy. The outcomes (O) studied were maternal, fetal and renal outcomes. The studies (S) were all studies reporting on pregnancy outcomes in women with DKD. As the data were expected to be heterogeneous, a narrative review of the results was planned.

Due to the lack of randomised controlled trials and the limited number and variability of control groups, no formal analysis of bias was performed.

Results

Study selection and general information (Table 1)

A total of 799 potentially relevant articles were identified after excluding duplicates. Of these, 731 were excluded after reviewing the abstract and 68 full-text articles were reviewed. Fifteen papers met the selection criteria and were included (Figure 1), 10 of which were retrospective studies and five were prospective. The studies were heterogeneous for size, study setting and years studied, ranging from 1988 to 2014. The majority were single-centre studies. Six studies included more than 50 women. The papers were from a range of countries including Denmark, Italy, UK, USA, Brazil, Israel and New Zealand. European countries, in particular Denmark, were the main source of data. Baseline characteristics were often inadequately described and varied between papers. The definitions of DKD varied widely and changed over time, with more recent studies including microalbuminuria (most commonly a urinary albumin of 30–299 mg/24 hours) and earlier studies including only 'overt' diabetic nephropathy: macroalbuminuria or macroproteinuria (typically more than 300–500 mg/24 hours proteinuria). One study divided participants into subgroups based on their renal function[10] and four divided them into subgroups based on micro- or macroalbuminuria.[11–14] Seven studies included controls, either diabetic or non-diabetic pregnant women or women with DKD who did not have a pregnancy. Study heterogeneity was significant, precluding the pooling of data and meta-analysis.

Baseline characteristics (Table 2)

Overall, this systematic review collected data on 843 women

Table 1. General information on studies

	Type	Years	Country	Aim	Definitions	Subgroups	Women	Pregnancies	Controls
Reece, 1990[19]	Retrospective	1970–1985	USA	To examine the effect of pregnancy on the rate of progression of DN	300 mg/day prior to 3rd trimester	NA	10	11	NA
Combs, 1993[20]	Retrospective	1982–1991	USA	To examine if pre-eclampsia in diabetic mothers is increased in incipient as well as overt nephropathy	>500 mg proteinuria/day	NA	62	62	No nephropathy Proteinuria 190–499 mg/24h
Hod, 1995[21]	Prospective	1990–1993	Israel	To examine whether treatment with ACE inhibitor pre-pregnancy improves pregnancy outcomes	>500 mg proteinuria/day	NA	8	8	NA
Kimmerle, 1995[4]	Retrospective	1982–1992	Germany	To study the effect of DKD on pregnancy and perinatal outcome, infant development and long-term function	>400 mg proteinuria/24h	Preserved renal function (CrCl >80 mL/min) Without preserved renal function (CrCl <80 mL/min)	Overall cohort 33	Overall cohort 40	110 in diabetic women without nephropathy
Gordon, 1996[22]	Retrospective	1988–1994	USA	To determine outcomes in pregnancies complicated by DN (white class F)	>400 mg/24h or CrCl <90 mL/min	NA	51	51	NA
Kaaja, 1996[23]	Prospective	1983–1985	Finland	To establish whether pregnancy affects long-term development and progression of retinopathy and nephropathy in diabetic women	White class F (CrCl >100 mL/min, creatinine <90 µmol/L	NA	6	9	4 women with DN without pregnancy
Mackie, 1996[10]	Retrospective	1985–1993	UK	To examine the effect of pregnancy on maternal renal function in women with DN	>500 mg/24h protein	Moderate renal impairment (serum creatinine >125 mmol/L) Mild renal impairment (serum creatinine <125 mmol/L)	6 12	11 13	NA
Miodovnik, 1996[24]	Prospective	1978–1991	USA	To examine whether pregnancy increases the risk of or accelerates the progression of DN	>500 mg/day proteinuria	NA	56	56	Diabetic pregnant women without nephropathy
Purdy, 1996[25]	Retrospective	1981–1993	USA	To determine whether pregnancy worsens renal function in women with DN and moderate-to-severe renal insufficiency	Serum creatinine >124 mmol/L	NA	11	11	11 women with similar renal function without pregnancy
Zhu, 1997[26]	Retrospective	1984–1996	Japan	To evaluate the outcomes of pregnancies complicated with diabetes mellitus	NR	NA	10	10	Pregnancies in women with diabetes without nephropathy
Reece, 1998[27]	Retrospective	1984–1990	USA	To report their 10-year experience in caring for patients with DN	>300 mg albumin or protein/24h	NA	27	27	NA
Bar, 1999[28]	Prospective	1990–1995	Israel	To examine the effect of pre-pregnancy captopril on renal function and on fetal-maternal outcome in DN	Proteinuria >500 mg/day	NA	24	24	NA
Biesenbach, 1999[11]	Retrospective	1982–1996	Austria	To evaluate the impact of pregnancy on the course of renal function in women with overt DN	Macroproteinuria >0.5 g protein-uria/24h	Increase in creatinine clearance during 1st two trimesters of pregnancy No increase in CrCl	12 5 7	14 6 8	NA
Dunne, 1999[29]	Retrospective	1990–1997	UK	To examine fetal/maternal outcomes in women with DN	>300 mg/24h or >1+ x 3	NA	18	21	NA
Biesenbach, 2000[30]	Retrospective	1985–1993	Austria	To evaluate perinatal complications and follow-up of infants of mothers with DN stage IV	500 mg/24h proteinuria	NA	10	10	NA
Ekbom, 2001[14]	Prospective	1996–2000	Denmark	Pregnancy outcome in T1 diabetic women with microalbuminuria	DKD >300 mg/24h Microalbuminuria 30–300 mg/24h	Microalbuminuria DN	26 11	26 11	Diabetic women with no microalbuminuria

Table 1. General information on studies (continued)

	Type	Years	Country	Aim	Definitions	Subgroups	Women	Pregnancies	Controls
Khoury, 2002[9]	Retrospective	NR	USA	To examine the association of renal function with maternal and fetal pregnancy outcome in women with DN	DN: proteinuria >500 mg/24h	Cr <1 mg/dL Cr 1–1.5 mg/dL Cr >1.5 mg/dL	58 (total cohort)	72 (total cohort) 49 13 10	NA
Rossing, 2002[18]	Retrospective	1970–1989	Denmark	To examine the long-term impact of pregnancy on the progression of DN	Albuminuria >300 mg/24h	NA	26	31	67 women without pregnancies
Bagg, 2003[31]	Prospective	1985–2000	New Zealand	To describe long-term maternal outcome after pregnancy in women with DN	>300 mg/24h albuminuria	NA	14	24	NA
Carr, 2006[7]	Retrospective	1986–2002	USA	To evaluate if hypertension in early pregnancy is associated with adverse perinatal outcome in women with DN	Proteinuria >0.3 g/24h	Above target BP (MAP >100 mmHg) Below target (MAP <100 mmHg)	43 22 21	43 22 21	NA
Nielson, 2006[32]	Retrospective	1995–2003	Denmark	To describe the impact of aggressive antihypertensive treatment in the prevalence of preterm delivery in women with DM	Albuminuria 30–300 mg/24h	1995–1999 2000–2003	26 20	26 20	NA
Nielsen, 2009[12]	Prospective	2004–2006	Denmark	To describe outcomes in microalbuminuria or DN after intensified anti-hypertensive therapy	DN: >300 mg albumin/24h Microalbuminuria: 30–299 mg albumin/24h	DN Microalbuminuria	7 10	7 10	100 women with normoalbuminuria 25 healthy pregnant women
Yogev, 2009[33]	Retrospective	2000–2007	Israel	To examine the factors associated with pregnancy complications in women with type 1 diabetes and DN	Protein 300 mg/24h pre or early pregnancy or serum creatinine >1.5	Non-complicated pregnancy Complicated pregnancy	15 31	15 31	NA
Jensen, 2010[34]	Prospective	1993–1999	Denmark	To describe microalbuminuria, pre-eclampsia, and preterm delivery in pregnant women with type 1 diabetes on a national level	Albuminuria 30–300 mg/24h	NA	84	84	Pregnant diabetic women without albuminuria
Bell, 2012[17]	Population-based cohort	1996–2008	UK	To quantify the risk of major congenital anomaly and to assess the influence of various risk factors including DN	Not reported	NA	60	60	Women with pregnancies complicated by congenital malformations without DN
Young, 2012[35]	Prospective	2010–2011	Brazil	To examine the effect of pregnancy on DN and the perinatal outcomes of diabetic pregnancies	Albuminuria >30 mg/24h	NA	11	11	32 pregnancies in diabetic women without DN
Damm, 2013[5]	Retrospective	2007–2012	Denmark	To evaluate the prevalence of DN and microalbuminuria in pregnant women with type 2 diabetes in comparison with type 1 diabetes and to describe pregnancy outcomes	Nephropathy: ACR >300 mg/g Microalbuminuria: ACR 30–299 mg/g	T2 nephropathy T1 nephropathy T2 microalbuminuria T1 microalbuminuria	5 11 10 15	5 11 10 15	NA
Piccoli, 2013[15]	Retrospective	2000–2012	Italy	To evaluate maternal and fetal outcomes in severe DN	Severe nephropathy: referred to nephrology clinic from diabetes in pregnancy clinic	NA	11	12	NA
Klemetti, 2015[16]	Retrospective	1988–2011	Finland	To analyse temporal changes in the glycaemic control, BP levels, markers of renal function as and perinatal outcomes of a population-based cohort of women with DN	Proteinuria >0.3 g/24h or dipstick 1+	1988–1999 2000–2011	65 43	65 43	NA
Seah, 2020[13]	Retrospective	2004–2014	Australia	Association between maternal renal function and pregnancy outcomes in type 1 and type 2 diabetes	Microalbuminuria: 3–300 mg/day or ACR of 3.4–35 Macroalbuminuria: >300 mg/day or ACR >35	Microalbuminuria Macroalbuminuria	198 with diabetes Number with nephropathy NR		119 pregnancies in healthy women

DN, diabetic nephropathy; Cr, creatinine

Table 2 Baseline characteristics

	Age	Ethnicity	Duration of diabetes (years)	Hypertension (%)	Retinopathy (%)	Baseline creatinine	Type of diabetes	Baseline HbA_{1c} (%)	Baseline proteinuria	Baseline eGFR (ml/min) or CrCl (ml/min)	Nulliparity (%)
Reece, 1990[19]	30	NR	NR	91	100	1.3 mg/dL			2.5 g/24h	NR	NR
Combs, 1993[20]	27.3	NR	14.3	39	37	0.91	T1	9.0	NR	56	NR
Hod, 1995[21]	25.6	NR	15.6	NR	37.5	0.8 mg/dL	T1	7.9	273 mg/24h	114	NR
Kimmerle, 1995[4]	29	NR	20	61	65	NR	NR	NR	2.1 g/24h	NR	NR
Gordon, 1996[22]	25.5	76% white	15	27	53	0.8	T1	NR	1.74 g /24	120	64
Kaaja, 1996[23]	35.5		21.7	11%	NR	NR	NR	NR	NR	NR	NR
Mackie, 1996[10]		NR			NR		NR	NR		NR	NR
Moderate renal impairment	30.5		17	16.6		160			3.8 g/24h		
Mild renal impairment	NR		NR	NR		NR			NR		
Miodovnik, 1996[24]	25.5	NR	14.7	40.8	39.2	NR	NR	9.8%	NR	NR	32
Purdy, 1996[25]	29	Mainly white	20	NR	NR	159	NR	NR	2.4 g/24h	NR	NR
Zhu, 1997[26]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Reece, 1998[27]	27		16.4	77	89	NR	NR	NR	NR	NR	NR
Bar, 1999[28]	26	NR	NR	46	37.5	0.82 mg/dL	T1	7.9	202 mg/24h	NR	NR
Biesenbach, 1999[11]	29	NR	18	NR	NR	111	NR	8.0	1.7	69	NR
	28	NR	17			96		8			
	29		20			122		8	1.1 g/24h	80	
									2.2 g/24h	61	
Dunne, 1999[29]	26.5	NR	19.5	11	NR	88.3	T1	9.7	NR	NR	NR
Biesenbach, 2000[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ekbom, 2001[14]		NR		NR		NR	T1			NR	
DN	29		19		77			8.1	69 mg/24h		50
Microalbuminuria	30		16		100			8.8	1120		55
Khoury, 2002[9]						NR					
Cr <1 mg/dL	26.3	14.3% black	15.4	12.2	24.5		T1	9.9	800 mg/24h	87.8 mL/min	51
Cr 1–1.5 mg/dL	28.3	0% black	16.5	69.2	46.2		T1	9.5	1796	79.2	61.5
Cr >1.5 mg/dL	29.0	30% black	15.6	90	80		T1	8.9	1606	41.5	60
Rossing, 2002[18]	24	NR	14	NR	NR	79 mmol/L	T1	NR	534 mg/24h	NR	NR
Bagg, 2003[31]	30	NR	18.5	NR	NR	0.07 mmol/L	T1 and T2	NR	NR	NR	NR
Carr, 2006[7]							T1				NR
Above target BP (MAP >100 mmHg)	29.5		16	59.1	63.6	0.85 mg/dL		8.1	1.65 g/24h	135.9 mL/min	
Below target (MAP <100 mmHg)	27.2		17.5	85.7	85.7	1.23 mg/dL		8	4.69	90.2 mL/min	
Nielson, 2006[32]		NR		NR	NR	NR	T1	NR		NR	NR
1995–1999	19		6.7						69 mg/24h		
2000–2003	18		6.8						74		
Nielsen, 2009[12]		NR					T1			NR	NR
Diabetic nephropathy	30		20	100	100	57		6.5	690 mg/24h		
Microalbuminuria	31		14	50	50	51		6.9	91		
Yogev, 2009[33]		NR					T1			NR	NR
Non-complicated pregnancy	31.8		18	80	53	1.08		7.1	53% none, 47% <20 mg/24h		
Complicated pregnancy	31.2		19.7	89	32	1.11		7.5	74% none, 13% <20 mg/24h, 6.5% 20–300 mg/24h, 6.5% >300 mg/24h		
Jensen, 2010[34]	27	NR	15	13	11	NR	T1	7.6	NR	68	NR
Bell, 2012[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Young, 2012[35]	28.3	45% Caucasian	12	72.7	54.6	0.8 mg/dL	81.2% T1	8.5	119 mg/24h	81 mL/min	27%
Damm, 2013[5]		NR							ACR	NR	
Type 2 DN	31		2	0	75	52	T2	6.8	474 mg/mol		50
Type 1 DN	32		19	64	56	61	T1	7	712		45
T2 microalbuminuria	31		2	0	20	40	T2	6.8	110		30
T1 microalbuminuria	31		22	60	85	51	T1	7.1	84. 5		67
Piccoli, 2013[15]	34.3	NR	22.6	66%	100%	0.98 mg/dL	T1	8.01%	1.6 g/24h	67 mL/min	NR
Klemetti, 2015[16]		NR									
1988–1999 group	29		19	34.4	50.8	82 µmol/L	T1	66 mmol/mol	1.5 g/24h	1.12	46.2
2000–2011 group	31		24	65.1	65.1	68 µmol/L	T1	69	0.8	1.74	60.5
Seah, 2020[13]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

DN, diabetic nephropathy; Cr, creatinine; NR, not reported.

with DKD experiencing 873 pregnancies. The mean age ranged from 24 to 34 years and the mean duration of diabetes ranged from 2 years (in two subgroups with type 2 diabetes)[11] to 22.6 years.[15] Where reported, both pre-pregnancy hypertension and retinopathy ranged from 11% in a cohort with microalbuminuria to 100% in women with overt proteinuria. Across the studies, 27–67% of women were nulliparous. Values for baseline creatinine, estimated glomerular filtration rate (eGFR) or creatinine clearance, proteinuria or albuminuria and HBA_{1c} were given either pre-pregnancy or in early pregnancy. One paper[16] divided its study participants into subgroups based on whether they had a complicated or uncomplicated pregnancy. These results are included in Tables 1–5 but have been excluded from the analysis below.

Maternal outcomes (Table 3)

There were high rates of pre-eclampsia and caesarean section, especially in those with impaired renal function, more severe proteinuria or both. Pre-eclampsia was commonly reported, ranging from 0%[12] in one subgroup of 10 women with microalbuminuria to 64% (IQR 33.3–42.5%);[17] compared to healthy women, women with diabetic kidney disease were more likely to develop pre-eclampsia (OR 5.5 (2.5 to 11.8)).[13] One study which included diabetic women without albuminuria, with microalbuminuria and macroalbuminuria reported pre-eclampsia in 6%, 42% and 64%, respectively.[14] Caesarean section was the most common method of delivery, ranging from 20% to 100% (IQR 69.2–90.0). No papers reported maternal death. One paper reported requirement for renal replacement therapy in one of 108 pregnancies.[18]

Fetal outcomes (Table 4)

The mean gestational age ranged from 32.5 weeks in a cohort with heavy proteinuria and impaired renal function[15] to 37.7 weeks in a subgroup with microalbuminuria (IQR 35.6–37.0).[12] The majority of births reported were premature, ranging from 20% in a subgroup with microalbuminuria[12] to 100% in a cohort with heavy proteinuria and impaired renal function (IQR 43.5–73.9).[15] Compared with healthy women, DKD was associated with premature delivery (microalbuminuria OR 3.9 (1.5 to 9.90), macroalbuminuria OR 3.9 (1.5 to 9.9)).[13] One study which included diabetic women with no albuminuria, with microalbuminuria and macroalbuminuria reported premature delivery in 35%, 62% and 91%, respectively.[12] Very premature births, variably reported as before 32 or 34 weeks, occurred in 0–46% of births (IQR 9.4–38.6). Compared with healthy women, DKD was associated with very premature delivery (OR 4.2 (1.9 to 9.5)).[13] The mean birth weight reported ranged from 1880 g to 3430 g. The 1880 g occurred in a subgroup with moderately impaired renal function and significant proteinuria[5] and the 3430 g occurred in a subgroup with microalbuminuria only.[12] The ranges for small for gestational age (SGA), where the neonate weighed less than the 10th centile for gestation, and large for gestational age (LGA), where the neonate weighed more than the 90th centile corrected for gestation, varied widely between the studies and were inconsistently reported. The IQR for SGA was 7.7–30.1% and for LGA was 9.1–33%. One study which included diabetic women with no albuminuria, with microalbuminuria and macroalbuminuria reported rates of SGA in 2%, 4% and 45%, respectively.[12] Neonatal intensive care unit (NICU) admission was common, reported in 26.2–75% of births (IQR 41.3–66.8), increased compared with women without DKD (OR 2.4 (1.2 to 4.6)).[13] Congenital abnormalities and perinatal deaths were uncommon, reported in 0–14% (IQR 0–9.2) and 0–14.2% (IQR 0–9.6), respectively. One study found that diabetic nephropathy (not further characterised) was associated with congenital abnormalities with an adjusted OR of 2.45 (1.14 to 5.25).[19]

Overall higher rates of prematurity, SGA and NICU admissions were noted in the groups with overt proteinuria and impaired renal function than in those with microalbuminuria or normal renal function. Rates were highest where both severe proteinuria and impaired renal function were present.

Blood pressure control

A number of studies designed to assess the impact of blood pressure on pregnancy outcomes were included. One observational study divided their cohort into two subgroups; one group had a mean arterial blood pressure (MAP) below a target of 100 mmHg and the other had a MAP of >100 mmHg.[5] They reported better maternal outcomes (27.3% pre-eclampsia versus 42%) and fetal outcomes (mean gestation 35.1 weeks versus 32.1 weeks) in the target MAP group.[5] Two further studies[12,20] reported an improvement in maternal and fetal outcomes with more intensive control of hypertension.

Renal outcomes (Table 5)

Only two of the papers published in the last 20 years reported on longer term renal outcomes. One paper, which followed 14 women with albuminuria >300 mg at the time of pregnancy for a mean of 6 years, reported 36% reached end-stage renal failure in that time. There was no control group.[21] The other paper followed 26 women with diabetic nephropathy who had pregnancies and 67 women with diabetic nephropathy without pregnancies for 10 years. The outcomes were similar in both groups, with a slightly higher incidence of end-stage renal failure in the group without pregnancy.[22]

Discussion

This systematic review of pregnancy outcomes and DKD showed that most women were relatively young, nulliparous and had a long duration of diabetes, usually type 1. There were high rates of maternal and fetal complications and these were more common in women with macroalbuminuria or impaired renal function. For comparison, in the general population pre-eclampsia affects 5% of women, 7.3% of babies arrive preterm (prior to 37 weeks),[23] 77% of birth weights are >3000 g[24] and 10.9–14.5% of babies are admitted to the NICU.[25] This review highlights high rates of Caesarean section in women with DKD. Women with diabetes already have higher rates of Caesarean

Table 3 Maternal outcomes

	Pre-eclampsia (%)	Caesarean section (%)	Maternal deaths (%)	Dialysis during pregnancy (%)	Miscarriage (%)	Abortion (%)
Reece, 1990[19]	NR	NR	NR	NR	Ex	Ex
Combs, 1993[20]	47	NR	NR	NR	Ex	Ex
Hod, 1995[21]	38	75	0	0	Ex	Ex
Kimmerle, 1995[4]	NR		NR	NR	0	10
Preserved renal function		80				
Non–preserved renal function		100				
Gordon, 1996[22]	53	80	NR	NR	7.8	3.9
Kaaja, 1996[23]	NR	NR	NR	NR	NR	NR
Mackie, 1996[10]	NR		NR	NR		
Moderate renal impairment		100			27	9
Mild renal impairment		100			0	7
Miodovnik, 1996[24]	76	76	NR	NR	Ex	Ex
Purdy, 1996[25]	NR	NR	NR	NR	NR	NR
Zhu, 1997[26]	40	90	NR	NR	NR	NR
Reece, 1998[27]	53	63	NR	NR	NR	NR
Bar, 1999[28]	46	62.5	NR	NR	Ex	Ex
Biesenbach, 1999[11]	57.1	50	NR	NR	Ex	Ex
Dunne, 1999[29]	50	90.5	NR	NR	Ex	Ex
Biesenbach, 2000[30]	60	60	NR	NR	NR	NR
Ekbom, 2001[14]		NR	NR	NR	NR	NR
DN	42					
Microalbuminuria	64					
Khoury, 2002[9]			0	0		NR
Cr <1 mg/dL	41	76.9			49	
Cr 1–1.5 mg/dL	33.3	91.7			13	
Cr >1.5 mg/dL	44.4	88.9			10%	
Rossing, 2002[18]	41	38.7	0	0	Ex	Ex
Bagg, 2003[31]	NR	83	NR	NR	NR	NR
Carr, 2006[7]			0	0	Ex	Ex
Above target BP (MAP >100 mmHg)	27.3	63.4				
Below target (MAP <100 mmHg)	42.9	76.2				
Nielson, 2006[32]	42	20				
Nielsen, 2009[12]		NR	NR	NR	Ex	Ex
Diabetic nephropathy	43					
Microalbuminuria	0					
Yogev, 2009[33]	NR		NR	NR		0
Non-complicated pregnancy		67			0	
Complicated pregnancy		78			10	
Jensen, 2010[34]	41	NR	NR	NR	Ex	Ex
Bell, 2012[17]	NR	NR	NR	NR	x	NR
Young, 2012[35]	63.6	NR	0	NR	Ex	Ex
Damm, 2013[5]			NR		Ex	Ex
Type 2 DN	40	60		0		
Type 1 DN	36	91		0		
T2 microalbuminuria	10	80		0		
T1 microalbuminuria	20	80		0		
Piccoli, 2013[15]	NR	75%	0	0	Ex	Ex
Klemetti, 2015[16]			NR		Excluded	Excluded
1988–1999 group	52.3	100		1%		
2000–2011 group	41.9	92.9				
Seah, 2020[13]		NR	NR	NR	Ex	Ex
Microalbuminuria	OR 5.7 (1.8 to 17.8)					
Macroalbuminuria	OR 5.5 (2.5 to 11.8)					

Cr, creatinine; DN, diabetic nephropathy; Ex, excluded; NR, not reported.

Table 4. Fetal outcomes

	Mean gestation (weeks)	Preterm delivery (%)	Very preterm delivery <34 weeks (%)	Weight (g)	SGA (%)	LGA (%)	NICU admission (%)	RDS (%)	IUD/ perinatal mortality (%)	Congenital abnormality (%)
Reece, 1990[19]	36.3	NR	NR	2557	NR	NR	NR	NR	0	0
Combs, 1993[20]	35.2	60	23	2788	NR	NR	NR	NR	NR	NR
Hod, 1995[21]	37	13	NR	2998	21.5	25	Nr	NR	0	0
Kimmerle, 1995[4]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gordon, 1996[22]	35.8	NR	15.5	2623	11	NR	89	NR	0	4
Kaaja, 1996[23]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mackie, 1996[19]		86	NR					NR	NR	
Moderate renal impairment	31			1970	14	14	100			14
Mild renal impairment	36			2600	8	8	42			0
Miodovnik, 1996[24]		57%	22	2745	9	22	NR	20	9	11
Purdy, 1996[25]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhu, 1997[26]	35.3	60	NR	2247	NR	NR	NR	NR	NR	NR
Reece, 1998[27]		26	NR	2687	9	NR	NR	NR	5	9
Bar, 1999[28]	NR	17	NR	2998	21	NR	4.2	NR	4.2	
Biesenbach, 1999[11]	34		64.2	1893	64.2	0	NR	21.4	14.2	7.1
Dunne, 1999[29]	NR	57.2	NR	2429	14	9.5	57.2	nr	9.5	4.7
Biesenbach, 2000[30]	36.3	NR	60	2250	50	0	NR	NR	10	NR
Ekbom, 2001[14]	NR					NR	NR	NR		
DN		62	23	3124	4				4	4
Microalbuminuria		91	45	2235	45				0	9
Khoury, 2002[9]		NR	<32 weeks	NR			NR			
Cr <1 mg/dL	35.7		7.7		7.7	12.8		15.4	5.1	12.9
Cr 1–1.5 mg/dL	34.3		16.7		8.3	0		41.7	0	0
Cr >1.5 mg/dL	33.3		44.4		33.3	33		33	11.1	0
Rossing, 2002[18]	37	NR	NR	2535	NR	NR	NR	NR	9.7	9.7
Bagg, 2003[31]	36		<35 weeks 46%	2950			75			12.5
Carr, 2006[7]			<32 weeks			NR	NR	NR		NR
Above target BP (MAP >100 mmHg)	35.1		4.6	2520	9.1				9.1	
Below target (MAP <100 mmHg)	32.8		38.1	1880	28.6				9.5	
Nielson, 2006[32]					NR	NR	NR	NR		
1995–1999	250 days	62	23	3124					4	4
2000–2003	259 days	40	0	3279					0	0
Nielsen, 2009[12]							NR	NR		
Diabetic nephropathy	258 days	71	14	2765	29	14			0	0
Microalbuminuria	264 days	20	0	3430	0	5			0	0
Yogev, 2009[33]			NR					NR		NR
Non-complicated pregnancy	37.8	0		3223	0	0	0		0	
Complicated pregnancy	32.4	32		3187	7	57	46		6	
Jensen, 2010[34]	260 days	36	16	3335	NR	50	NR	19	5	NR
Bell, 2012[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	Unadjusted OR 2.78 (1.37 to 5.64) Adjusted OR 2.45 (1.14 to 5.25)
Young, 2012[35]	36	63.6	NR	2710	40	9.1	NR	NR	0	20
Damm, 2013[5]								NR	NR	NR
Type 2 DN	250 days	60	40	2460	40	0	60			
Type 1 DN	249 days	82	27	2506	36	18	64			
T2 microalbuminuria	260 days	30	10	3355	20	30	44			
T1 microalbuminuria	259 days	47	7	3229	7	53	33			
Piccoli, 2013[15]	32.5	100	58	1919	7.6	NR	85	NR	20	0
Klemetti, 2015[16]			<32 weeks							
1988–1999 group	254 days	70.8	13.8	2978	15.4	35.4	26.2		4.6	9.5% of total cohort
2000–2011 group	246 days	76.7	20.9	2694	23.3	27.9	48.8		4.7	
Seah, 2020[13]	NR			NR	NR	NR	–	NR	NR	NR
Microalbuminuria group		OR 3.9 (1.5 to 9.9)								
Macroalbuminuria group		OR 3.5 (1.6 to 7.7)	OR 4.2 (1.9 to 9.5)				OR 2.4 (1.2 to 4.6)			

Cr, creatinine; DN, diabetic nephropathy; LGA, large for gestational age; NICU, neonatal intensive care unit; NR, not reported; RDS, respiratory distress syndrome; SGA, small for gestational age.

Table 5 Long-term renal outcomes

	Follow-up post delivery	Worsening proteinuria	Worsening renal function	Doubling creatinine	Mean eGFR decline/year	ESRF
Reece, 1990[19]	29 months	27%	27%	9%	0	0
Combs, 1993[20]	NR	NR	NR	NR	NR	NR
Hod, 1995[21]	NR	NR	NR	NR	NR	NR
Kimmerle, 1995[4]	NR	NR	NR	NR	NR	NR
Gordon, 1996[22] Subgroup <1 g proteinuria and CrCl >90 mL/min	2.8 years	No difference between groups	NR	NR	15.6 mL/min decline/year 6.6 mL/min vs 18.9 for rest of cohort	8.5%
Kaaja, 1996[23] With pregnancy Without pregnancy	5–9 years	 4/6 3/4	 2/6 1/4	NR	NR	 1/6 1/4
Mackie, 1996[10] Moderate renal impairment group (n=6) Preserved renal function (n=11)	6 months–8 years	NR	 50% (3) 9% (1)	NR	NR	 50% (3) 9% (1)
Miodovnik, 1996[24] Controls (diabetes and pregnancy, no DN)	9.5 years 9.1 years	NR	NR	NR	8–10 mL/year	26% 0.7%
Purdy, 1996[25]	35–138 months	82%	45%	NR	NR	6%
Zhu, 1997[26]	NR	NR	NR	NR	NR	NR
Reece, 1998[2]	NR	NR	NR	NR	NR	NR
Bar, 1999[28]	2 years	NR	0	0	NR	Nil
Biesenbach, 1999[11] Low clearance group Normal clearance group	6 months	 2.2 g/24 h to 2.8 g/24 h No change	 87% 0%	 61 mL/min to 38 mL/min 80 mL/min to 9 mL/min	 NR No change	 NR NR
Dunne, 1999[29]	2	NR	No difference	No difference	NR	5%
Biesenbach, 2000[30]	NR	NR	NR	NR	NR	NR
Ekbom, 2001[14]	NR	NR	NR	NR	NR	NR
Khoury, 2002[9]	NR	NR	NR	NR	NR	NR
Rossing, 2002[18] Women with DN and pregnancy Controls (women with DN without pregnancy)	10 years	 534 to 786 mg/24h 597 to 882 mg/24h	NR	 31% 33%	 2.2 mL/min 3.6 mL/min	 19% 24%
Bagg, 2003[31]	6 years	NR	NR	NR	NR	36%
Carr, 2006[7]	NR	NR	NR	NR	NR	NR
Nielson, 2006[32]	NR	NR	NR	NR	NR	NR
Nielsen, 2009[12]	NR	NR	NR	NR	NR	NR
Yogev, 2009[33]	NR	NR	NR	NR	NR	NR
Jensen, 2010[34]	NR	NR	NR	NR	NR	NR
Bell, 2012[17]	NR	NR	NR	NR	NR	NR
Young, 2012[35]	NR	NR	NR	NR	NR	NR
Damm, 2013[5]	NR	NR	NR	NR	NR	NR
Piccoli, 2013[15]	NR	NR	NR	NR	NR	NR
Klemetti, 2015[16]	NR	NR	NR	NR	NR	NR
Seah, 2020[13]	NR	NR	NR	NR	NR	NR

CrCl, creatinine clearance; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; ESRF, end stage renal failure. NR, not reported.

Table 6 Management of diabetic kidney disease in pregnancy

Pre-pregnancy	• Women with diabetes should have an assessment of their renal function (including proteinuria) prior to stopping contraception • Women with a creatinine >120 mmol/L, albuminuria >30 mg/mmol or eGFR <45 mL/min should be referred to a nephrologist prior to pregnancy • Women with diabetic nephropathy should be offered pre-pregnancy counselling to inform them of potential adverse pregnancy outcomes and to allow optimisation of blood pressure, glycaemic control and proteinuria prior to pregnancy • They should remain on angiotensin converting enzyme inhibitors until conception, with regular pregnancy testing during attempts to conceive • The HbA_{1c} should be below 48 mmol/mol prior to conception (if achievable without causing problematic hypoglycaemia) • High dose folic acid 5 mg should be started 3 months prior to conception
During pregnancy	• Women with a creatinine >120 mmol/L, albuminuria >30 mg/mmol or PCR >50 mg/mmol should see a nephrologist during pregnancy (Note: eGFR should not be used during pregnancy) • They should have regular MDT visits throughout gestation (every 1–2 weeks) • They should be offered low-dose aspirin (75–150 mg) before 16 weeks of gestation as pre-eclampsia prophylaxis • Women with nephrotic range proteinuria (PCR >300 mg/mmol or ACR >250 mg/mmol should be offered prophylactic low molecular weight heparin during pregnancy and the postpartum period • Target blood pressure of 110–130 mmHg (systolic) and 70–90 mmHg (diastolic) should be used • The creatinine and ACR/PCR should be checked at least 4-weekly and at least fortnightly from 32 weeks of gestation
Post-partum	• Restart RAAS blockade post-partum as soon as renal function is stable. In breastfeeding, enalapril and captopril are the preferred ACE inhibitors, and angiotensin receptor blockade is not advised until breastfeeding cessation • Ensure follow-up with nephrologist post-partum (and with the diabetes services if not already engaged)

ACR, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; PCR, protein:creatinine ratio; RAAS, renin angiotensin aldosterone system.

section than the general population (46% versus 12%).[3] This risk is higher again in women with DKD. The additive risks of pre-eclampsia, growth restriction and concern over loss of kidney function likely contribute to the high rate of prematurity.

Historically, women with diabetic nephropathy had high rates of fetal loss, obstetric complications and progression to end-stage renal failure in pregnancy. In recent years, with improved diagnosis and management of DKD before and during pregnancy, outcomes have improved. However, the risk of complications is much higher than in healthy women and women with diabetes without kidney disease, as detailed above. The papers included in this review have informed our current knowledge and have been incorporated in a number of comprehensive guidelines including the National Institute for Health and Care Excellence and American Diabetes Association guidelines on management of diabetes in pregnancy and the Renal Association guidelines on Pregnancy and Renal Disease.[26–28] Important aspects of management include pre-pregnancy counselling, close multidisciplinary antenatal monitoring with strict blood pressure control, pre-eclampsia prophylaxis and consideration of thromboprophylaxis and early reintroduction of ACE inhibitors and ensuring appropriate follow-up postnatally. Key management points are summarised in Table 6.

This systematic review was limited by the quality of the studies included; they were most often retrospective, small and monocentric and may have been subject to selection or reporting biases. As a result of these very heterogeneous studies, the results reported varied widely between studies. The variations in the definition of DKD used, the evolving definition of pre-eclampsia and the notorious difficulty diagnosing pre-eclampsia in women with pre-existing hypertension and proteinuria are likely also to have affected the reported outcomes. As diabetes and DKD are common conditions, it is vital for women and their doctors from different disciplines, including obstetrics, endocrinology and nephrology, to be fully aware of the risks associated with pregnancy. This will empower women to make a fully informed decision when considering pregnancy and enable better obstetric and renal care, leading to a safer pregnancy with better outcomes.

Key messages

- The studies performed looking at diabetic kidney disease (DKD) and pregnancy are heterogenous and vary in the definitions used and the outcomes measured
- Adverse pregnancy outcomes are frequently encountered in women with DKD.
- Adverse pregnancy outcomes are more common in diabetic women with macroalbuminuria and impaired renal function
- Pregnancy outcomes in women with DKD have improved over the last few decades
- Important aspects of management include:
  - pre-pregnancy counselling
  - antenatal close multidisciplinary monitoring with strict blood pressure control, preeclampsia prophylaxis and consideration of thromboprophylaxis
  - postnatal - early reintroduction of ace-inhibitors and appropriate follow up postnatally

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References

1. Confidential Enquiry into Maternal and Child Health. Diabetes in pregnancy: are we providing the best care? Findings of a national enquiry.

England, Wales and Northern Ireland. London: Confidential Enquiry into Maternal and Child Health, 2007.
2. Ringholm L, Damm JA, Vestgaard M, Damm P, Mathiesen ER. Diabetic nephropathy in women with preexisting diabetes: from pregnancy planning to breastfeeding. *Curr Diab Rep* 2016;**16**(2):12. https://doi.org/10.1007/s11892-015-0705-3
3. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. D*iabetes Care* 2009;**32**(11):2005–9. https://doi.org/10.2337/dc09-0656
4. White P. Pregnancy complicating diabetes. *J Am Med Assoc* 1945; **128**(3):181–2.
5. Carr D, Koontz G, Gardella C, *et al*. Diabetic nephropathy in pregnancy: suboptimal hypertensive control associated with preterm delivery. *Am J Hypertens* 2006;**19**(5):513–19. https://doi.org/10.1016/j.amjhyper.2005.12.010
6. Kimmerle R, Zass RP, Cupisti S, *et al*. Pregnancies in women with diabetic nephropathy: long-term outcome for mother and child. *Diabetologia* 1995;**38**(2):227–35.
7. Bramham K. Diabetic nephropathy and pregnancy. *Semin Nephrol* 2017;**37**(4):362–9. https://doi.org/10.1016/j.semnephrol.2017.05.008
8. Ekbom P. Pre-pregnancy microalbuminuria predicts pre-eclampsia in insulin-dependent diabetes mellitus. *Lancet* 1999;**353**(9150):377. https://doi.org/10.1016/s0140-6736(05)74949-7
9. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;**4**(1):1.
10. Khoury JC, Miodovnik M, LeMasters G, Sibai B. Pregnancy outcome and progression of diabetic nephropathy. What's next? *J Matern Fetal Neonatal Med* 2002;**11**:238–44. https://doi.org/10.1080/jmf.11.4.238.244
11. Damm JA, Asbjornsdottir B, Callesen NF, *et al*. Diabetic nephropathy and microalbuminuria in pregnant women with type 1 and type 2 diabetes: prevalence, antihypertensive strategy, and pregnancy outcome. *Diabetes Care* 2013;**36**(11):3489–94. https://doi.org/10.2337/dc13-1031
12. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? *Diabetes Care* 2009; **32**(1):38–44. https://doi.org/10.2337/dc08-1526
13. Seah J, Kam NM, Wong L, *et al*. The association between maternal renal function and pregnancy outcomes in type 1 and type 2 diabetes. *Diabetes Res Clin Pract* 2020;**165**:108225. https://doi.org/10.1016/j.diabres.2020.108225
14. Ekbom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Mølvig J, Mathiesen ER. Pregnancy outcome in type 1 diabetic women with microalbuminuria. *Diabetes Care* 2001;**24**(10):1739–44. https://doi.org/10.2337/diacare.24.10.1739
15. Piccoli GB, Tavassoli E, Melluzza C, *et al*. Severe diabetic nephropathy in type 1 diabetes and pregnancy - a case series. *Rev Diabet Stud* 2013;**10**(1):68–78. https://doi.org/10.1900/RDS.2013.10.68
16. Yogev Y, Chen R, Ben-Haroush A, Hod M, Bar J. Maternal overweight and pregnancy outcome in women with type-1 diabetes mellitus and different degrees of nephropathy. *J Matern Fetal Neonatal Med* 2010;**23**(9):999–1003. https://doi.org/10.3109/14767050903544744
17. Young EC, Pires MLE, Marques LPJ, de Oliveira JEP, Zajdenverg L. Effects of pregnancy on the onset and progression of diabetic nephropathy and of diabetic nephropathy on pregnancy outcomes. *Diabetes Metab Syndr* 2011;**5**(3):137–42. https://doi.org/10.1016/j.dsx.2012.02.013
18. Klemetti MM, Laivuori H, Tikkanen M, Nuutila M, Hiilesmaa V, Teramo K. Obstetric and perinatal outcome in type 1 diabetes patients with diabetic nephropathy during 1988–2011. *Diabetologia* 2015;**58**(4):678–86. https://doi.org/10.1007/s00125-014-3488-1
19. Bell R, Glinianaia SV, Tennant PWG, Bilous RW, Rankin J. Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. *Diabetologia* 2012;**55**(4):936–47. https://doi.org/10.1007/s00125-012-2455-y
20. Nielsen LR, Muller C, Damm P, Mathiesen ER. Reduced prevalence of early preterm delivery in women with type 1 diabetes and microalbuminuria-possible effect of early antihypertensive treatment during pregnancy. *Diabet Med* 2006;**23**(4):426–31. https://doi.org/10.1111/j.1464-5491.2006.01831.x
21. Bagg W, Neale L, Henley P, MacPherson P, Cundy T. Long-term maternal outcome after pregnancy in women with diabetic nephropathy. *N Z Med J* 2003;**116**(1180):U566.
22. Rossing K, Jacobsen P, Hommel E, *et al*. Pregnancy and progression of diabetic nephropathy. *Diabetologia* 2002;**45**(1):36–41. https://doi.org/10.1007/s125-002-8242-4
23. National Institute for Health and Care Excellence (NICE). Preterm labour and birth. NICE Guideline [NG25]. 2015 (updated 2019). Available from: https://www.nice.org.uk/guidance/ng25/chapter/context
24. NHS Digital. NHS maternity statistics, England 2019–20. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2019-20
25. Braun D, Braun E, Chiu V, *et al*. Trends in Neonatal intensive care unit utilization in a large integrated health care system. *JAMA Netw Open [Internet].* 2020;**3**(6):e205239. https://doi.org/10.1001/jamanetworkopen.2020.5239
26. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management from preconception to the postnatal period. NICE Guideline [NG3]. 2015 (updated 2020). Available from: https://www.nice.org.uk/guidance/ng3
27. Wiles K, Chappell L, Clark K, *et al*. Clinical practice guideline on pregnancy and renal disease. *BMC Nephrol* 2019;**20**(1):401. https://doi.org/10.1186/s12882-019-1560-2
28. American Diabetes Association. 14. Management of Diabetes in Pregnancy: standards of medical care in diabetes – 2020. *Diabetes Care* 2020;**43**(Suppl 1):S183–92. https://doi.org/10.2337/dc20-S014