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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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 and four divided them into subgroups based on micro- or macroalbuminuria. 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 |
|-----------------|-----------|----------|----------------------------------------------------------------------|--------------------------------------------------|--------------------------------------|-------|-------------|----------|
| Prospective     | 1990–1993 | Israel   | To examine whether treatment with ACE inhibitor pre-pregnancy improves pregnancy outcomes | >500 mg proteinuria/day NA                        | 8 8 NA                               |       |             |          |
| 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 <80 mL/min, creatinine <90 μmol/L) | 6 9 4 women with DN without pregnancy |       |             |          |
| Retrospective   | 1985–1993 | UK       | To examine the effect of pregnancy on maternal renal function in women with DN | >500 mg/24h proteinuria Moderate renal impairment (serum creatinine >125 mmol/L), Mild renal impairment (serum creatinine <125 mmol/L) | 6 11 NA                              |       |             |          |
| 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 |       |             |          |
| Prospective     | 1990–1995 | Israel   | To examine the effect of pre-pregnancy captopril on renal function and on fetal-maternal outcome in ODN | Proteinuria >500 mg/day NA                         | 24 24 NA                              |       |             |          |
| 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 proteinuria/24h            | 5 7 12 NA                              |       |             |          |
| Retrospective   | 1990–1997 | UK       | To examine fetal-maternal outcomes in women with DN | >300 mg/24h or 1x3 NA NA                          | 18 21 NA                              |       |             |          |
| Retrospective   | 1985–1993 | Austria  | To evaluate perinatal complications and follow-up of infants of mothers with DN stage IV | Proteinuria >500 mg/24h NA                         | 10 10 NA                              |       |             |          |
| Prospective     | 1996–2000 | Denmark  | Pregnancy outcome in T1 diabetic women with microalbuminuria | DKD >300 mg/24h, Microalbuminuria 30–300 mg/24h    | 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  | Retrospective| NR      | USA To examine the association of renal function with maternal and fetal pregnancy outcome in women with DN | DN: proteinuria >100 mg/24h Cr <1 mg/dL Cr 1–1.5 mg/dL Cr >1.5 mg/dL | 58 (total cohort) 72 (total pregnant cohort) 49 13 10 | NA    |             |          |
| Rossing, 2002 | 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    | 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    | 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 | 43 22 | NA |
| Nielsen, 2006 | Retrospective| 1995–2003| Denmark To describe the impact of aggressive antihypertensive treatment in the prevalence of preterm delivery in women with DN | Albuminuria 30–300 mg/24h 1995–1999 2000–2003 | 26 | 20 | 26 20 | NA |
| Nielsen, 2009 | 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   | Retrospective| 2000–2007| Israel To examine the factors associated with pregnancy complications in women with type 1 diabetes and women with DN | Protein 300 mg/24h pre or early pregnancy or serum creatinine >1.5 Non-complicated pregnancy Complicated pregnancy | 15 | 15 | NA |
| Jensen, 2010  | 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    | 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   | 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    | 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 >30 mg/g Microalbuminuria: ACR 30–299 mg/g T2 nephropathy T1 nephropathy T2 microalbuminuria T1 microalbuminuria | 5 11 15 | 5 11 15 | NA |
| Piccoli, 2013 | Retrospective| 2000–2012| Italy To evaluate maternal and fetal outcomes in severe DN | Severe nephropathy: referred to nephrology clinic from diabes clinic in pregnancy clinic | NA | 11 | 12 | NA |
| Klemetti, 2015 | 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    | 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 Microalbuminuria: >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

| Ref.          | Age | Ethnicity | Duration of diabetes (years) | Hypertension (%) | Renal failure (%) | Baseline serum creatinine (mg/dL) | Type of diabetes | Baseline HbA1c (%) | Baseline proteinuria (mg/24 h) | Baseline eGFR (ml/min) or GFR (ml/min) | Nulliparity (%) |
|---------------|-----|-----------|------------------------------|------------------|------------------|-----------------------------------|------------------|-------------------|----------------------------------|----------------------------------------|-----------------|
| Reece, 1990   | 30  | NR        | NR                           | 91               | NR               | 100                               | 1.3 mg/dL        | T1                | 2.5 g/24h                     | NR                                      | NR              |
| Combs, 1993   | 27.3| NR        | NR                           | 14.3             | NR               | 39                               | 0.91             | T1                | 9.0 g/24h                     | NR                                      | 56              |
| Hod, 1995     | 25.6| NR        | NR                           | 15.6             | NR               | 37.5                              | 0.8 mg/dL        | T1                | 7.9 g/24h                     | 114                                      | NR              |
| Kimeterle, 1994| 29  | NR        | NR                           | 20               | 61               | 65                               | NR               | NR                | 2.1 g/24h                     | NR                                      | NR              |
| Gordon, 1996  | 25.5| 76% white | NR                           | 15               | 27               | 53                               | 0.8              | T1                | NR                            | 1.7 g/24h                               | 120             |
| Kajaa, 1996   | 35.5| NR        | NR                           | 21.7             | 11               | NR                               | NR               | NR                | NR                            | NR                                      | NR              |
| Mackie, 1996  | 30.5| NR        | NR                           | 17               | 16               | 160                              | NR               | NR                | 3.8 g/24h                     | NR                                      | NR              |
| Naidovnik, 1996| 25.5| NR        | 14.7                         | 40.8             | NR               | 39.2                              | NR               | NR                | 9.8%                          | NR                                      | NR              |
| Purdy, 1996   | 29  | Mainly white| 20                          | NR               | 159              | 15                               | NR               | NR                | 2.4 g/24h                     | NR                                      | NR              |
| Zhu, 1997     | 27  | NR        | NR                           | 16.4             | 77               | 89                               | NR               | NR                | NR                            | NR                                      | NR              |
| Reece, 1998   | 26  | NR        | NR                           | 46               | NR               | 37.5                              | 0.82 mg/dL       | T1                | 7.9 g/24h                     | 202 g/24h                               | NR              |
| Bar, 1999     | 28  | NR        | NR                           | 18               | 17               | 20                               | NR               | 111               | 8.0                         | 1.7                                      | 69              |
| Nielsen, 1999 | 29  | NR        | NR                           | 17               | 20               | NR                               | 96               | NR                | 122                             | NR                                      | NR              |
| Dunne, 1999   | 26.5| NR        | NR                           | 19.5             | 11               | NR                               | 88.3             | T1                | 9.7 g/24h                     | NR                                      | NR              |
| Biesensch, 2000| 29         | NR        | NR                           | NR               | NR               | NR                               | NR               | NR                | NR                            | NR                                      | NR              |
| Edison, 2001  | 29  | NR        | NR                           | 19               | 16               | NR                               | T1               | 8.1               | 69 g/24h                      | 1120                                    | NR              |
| Khoury, 2002  | 26.3| 14.3% black| 15.4                         | 12.2             | 24.5             | NR                               | T1               | 9.9               | 800 g/24h                     | NR                                      | 51              |
| Rossing, 2002 | 24  | NR        | NR                           | NR               | NR               | 79 mmol/L                       | T1               | NR                | 534 g/24h                     | NR                                      | NR              |
| Bagg, 2003    | 30  | NR        | NR                           | 18.5             | NR               | 0.07 mmol/L                      | T1 and T2        | NR                | NR                            | NR                                      | NR              |
| Carr, 2006    | 29.5| 16          | 59.1                         | 63.6             | 0.85 mg/dL        | NR                               | T1               | 8.1               | 1.65 g/24h                     | 135.9 mL/min               | NR              |
| Nielson, 2006 | 19  | NR        | NR                           | 6.7              | NR               | 6.8                             | NR               | NR                | 69 g/24h                      | 74                                      | NR              |
| Nielson, 2007 | 30  | NR        | NR                           | 20               | 100              | 100                             | 57               | T1                | 6.5 g/24h                     | 690 g/24h                               | NR              |
| Yogey, 2009   | 31.8| 18          | 80                           | 53               | 1.08             | T1                               | T1               | 7.1               | 53% none, 47% <20 g/24h, 74% none, 13% <10 g/24h, 6.5% 20–300 mg/24h, 6.5% >300 mg/24h | NR                                      | NR              |
| Jensen, 2010  | 27  | NR        | NR                           | 15               | 13               | 11                               | NR               | 7.6               | 119 mg/24h                     | 81 mL/min                               | 27%             |
| Bell, 2012    | 28.3| 45% Caucasian| 12                         | 72.7             | 54.6             | 0.8 mg/dL                        | 82.1% T1        | 8.5               | 119 mg/24h                     | 81 mL/min                               | NR              |
| Damm, 2013    | 31  | NR        | NR                           | 2                | 0                | 75                               | 52               | T2                | 6.8 g/24h                     | 474 mg/mmol                             | NR              |
| Piccoli, 2013 | 34.3| NR        | 22.6                         | 66%              | 100%             | 0.98 mg/dL                       | T1               | 8.01%            | 1.6 g/24h                     | 67 mL/min                               | NR              |
| Klemetti, 2015 | 29 | NR        | NR                           | 19               | 34.4             | 50.8                             | 82 mmol/L        | T1               | 66 mmol/L 1.5 g/24h          | 1.12                                    | 46.2            |
| Seah, 2020    | 31  | NR        | NR                           | 24               | 65.1             | 65.1                             | 68 mmol/L        | T1               | 69 g/24h                      | 60.5                                    | 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)\textsuperscript{11} to 22.6 years.\textsuperscript{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\textsubscript{1c} were given either pre-pregnancy or in early pregnancy. One paper\textsuperscript{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%\textsuperscript{12} in one subgroup of 10 women with microalbuminuria to 64% (IQR 33.3–42.5%);\textsuperscript{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)).\textsuperscript{13} One study which included diabetic women without albuminuria, with microalbuminuria and macroalbuminuria reported pre-eclampsia in 6%, 42% and 64%, respectively.\textsuperscript{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.\textsuperscript{18}

**Fetal outcomes (Table 4)**

The mean gestational age ranged from 32.5 weeks in a cohort with heavy proteinuria and impaired renal function\textsuperscript{11} to 37.7 weeks in a subgroup with microalbuminuria (IQR 35.6–37.0).\textsuperscript{12} The majority of births reported were premature, ranging from 20% in a subgroup with microalbuminuria\textsuperscript{12} to 100% in a cohort with heavy proteinuria and impaired renal function (IQR 43.5–73.9).\textsuperscript{15} Compared with healthy women, DKD was associated with premature delivery (microalbuminuria OR 3.9 (1.5 to 9.9), macroalbuminuria OR 3.9 (1.5 to 9.9)).\textsuperscript{13} One study which included diabetic women with no albuminuria, with microalbuminuria and macroalbuminuria reported premature delivery in 35%, 62% and 91%, respectively.\textsuperscript{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)).\textsuperscript{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\textsuperscript{1} and the 3430 g occurred in a subgroup with microalbuminuria only.\textsuperscript{11} 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.\textsuperscript{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)).\textsuperscript{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).\textsuperscript{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.\textsuperscript{3} 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.\textsuperscript{5} Two further studies\textsuperscript{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.\textsuperscript{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.\textsuperscript{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),\textsuperscript{23} 77% of birth weights are $>3000$ g\textsuperscript{4} and 10.9–14.5% of babies are admitted to the NICU.\textsuperscript{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            | NR                | NR                    | NR                  | NR                            | Ex              | Ex           |
| Combs, 1993            | 47                | NR                    | NR                  | NR                            | Ex              | Ex           |
| Hod, 1995              | 38                | 75                    | 0                   | 0                             | Ex              | Ex           |
| Kimmerle, 1995         | NR                | 80                    | NR                  | NR                            | 0              | 10           |
| Gordon, 1996           | 53                | 80                    | NR                  | NR                            | 7.8             | 3.9          |
| Kaaja, 1996            | NR                | NR                    | NR                  | NR                            | NR              | NR           |
| Mackie, 1996           | NR                | 100                   | NR                  | NR                            | NR              | NR           |
| Miodovnik, 1996        | 76                | 76                    | NR                  | NR                            | Ex              | Ex           |
| Purdy, 1996            | NR                | NR                    | NR                  | NR                            | NR              | NR           |
| Zhu, 1997              | 40                | 90                    | NR                  | NR                            | NR              | NR           |
| Reece, 1998            | 53                | 63                    | NR                  | NR                            | NR              | NR           |
| Bar, 1999              | 46                | 62.5                  | NR                  | NR                            | 27              | 0            |
| Biesenbach, 1999       | 57.1              | 50                    | NR                  | NR                            | Ex              | Ex           |
| Dunne, 1999            | 50                | 90.5                  | NR                  | NR                            | Ex              | Ex           |
| Biesenbach, 2000       | 60                | 60                    | NR                  | NR                            | NR              | NR           |
| Ekborn, 2001           | 42                | NR                    | NR                  | NR                            | NR              | NR           |
| Khoury, 2002           | Cr <1 mg/dL       | 76.9                  | 0                   | 0                             | 49              | Ex           |
|                        | Cr 1–1.5 mg/dL     | 91.7                  | 0                   | 0                             | 13              | Ex           |
|                        | Cr >1.5 mg/dL      | 88.9                  | 0                   | 0                             | 10%             |              |
| Rossing, 2002          | 41                | 38.7                  | 0                   | 0                             | Ex              | Ex           |
| Bagg, 2003             | NR                | 83                    | NR                  | NR                            | NR              | NR           |
| Carr, 2006             | Above target BP (MAP >100 mmHg) | 27.3 | 63.4 | NR | NR | NR | NR |
|                        | Below target (MAP <100 mmHg) | 42.9 | 76.2 | 0 0 | Ex | Ex |
| Nielsen, 2006          | 42                | 20                    | NR                  | NR                            | NR              | Ex           |
| Nielsen, 2009          | Diabetic nephropathy | 43 0 | NR | NR | NR | Ex | Ex |
| Yogeu, 2009            | Non-complicated pregnancy | NR 67 | NR | NR | NR | 0 0 |
|                        | Complicated pregnancy | 78 0 | NR | NR | NR | 0 0 |
| Jensen, 2010           | 41                | NR                    | NR                  | NR                            | Ex              | Ex           |
| Bell, 2012             | NR                | NR                    | NR                  | NR                            | x               | NR           |
| Young, 2012            | 63.6              | NR                    | 0                   | NR                            | Ex              | Ex           |
| Damm, 2013             | Type 2 DN         | 40                    | NR                  | 0                             | Ex              | Ex           |
|                        | Type 1 DN         | 36                    | 60                  | 0                             | 0               | 0            |
|                        | T2 microalbuminuria | 10 80            | 91                 | 0                             | 0               | 0            |
|                        | T1 microalbuminuria | 20 80            | 80                 | 0                             | 0               | 0            |
| Piccoli, 2013          | NR                | 75%                   | 0                   | 0                             | Ex              | Ex           |
| Klemetti, 2015         | 52.3              | 41.9                  | NR                  | 1%                            | Excluded        | Excluded     |
|                        | 1988–1999 group   | 100                  | 92.9               | NR                            | Excluded        | Excluded     |
|                        | 2000–2011 group   | 52.3                  | 41.9               | NR                            | Excluded        | Excluded     |
| Seah, 2020             | Microalbuminuria  | NR                    | NR                  | NR                            | Ex              | Ex           |
|                        | Macroalbuminuria  | OR 5.7 (1.8 to 17.8) | OR 5.5 (2.5 to 11.8) | NR                            | NR              | Ex           |

Cr, creatinine; DN, diabetic nephropathy; Ex, excluded; NR, not reported.
### Table 4. Fetal outcomes

| Study/Description | Mean gestation (weeks) | Preterm delivery (%) | Very preterm delivery <34 weeks (%) | Weight (g) | SGA (%) | LGA (%) | NICU admission (%) | RDS (%) | IUD/perinatal mortality (%) | Congenital abnormality (%) |
|-------------------|------------------------|-----------------------|--------------------------------------|-----------|---------|---------|-------------------|--------|---------------------------|---------------------------|
| Reece, 1990<sup>10</sup> | 36.3 | NR | NR | 2557 | NR | NR | NR | NR | NR | 0 | 0 |
| Combs, 1993<sup>20</sup> | 35.2 | 60 | 23 | 2788 | NR | NR | NR | NR | NR | NR | NR |
| Hod, 1995<sup>11</sup> | 37 | 13 | NR | 2998 | 21.5 | 25 | NR | NR | NR | 0 | 0 |
| Kimmerle, 1994<sup>4</sup> | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Gordon, 1996<sup>8</sup> | 35.8 | NR | 15.5 | 2623 | 11 | NR | 89 | NR | 0 | 4 |
| Kaja, 1996<sup>12</sup> | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Mackie, 1996<sup>13</sup> | Moderate renal impairment | Mild renal impairment | 31 | 69 | 20 | 3 | 1 | 14 | 2 | 4 |
| Miodovnik, 1996<sup>14</sup> | 57% | <32 weeks | 2745 | 9 | 22 | NR | 20 | 9 | 11 |
| Purdy, 1996<sup>15</sup> | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Zhu, 1997<sup>16</sup> | 35.3 | 60 | NR | 2247 | NR | NR | NR | NR | NR | NR |
| Reece, 1998<sup>17</sup> | 26 | NR | NR | 2687 | 9 | NR | NR | NR | 5 | 9 |
| Bar, 1999<sup>18</sup> | NR | 17 | NR | 2998 | 21 | NR | 4.2 | NR | 4.2 |
| Biesenbach, 1999<sup>1</sup> | 34 | 64.2 | 1893 | 64.2 | 0 | NR | 21.4 | 14.2 | 7.1 |
| Dunne, 1999<sup>19</sup> | NR | 57.2 | NR | 2429 | 14 | 9.5 | 57.2 | nr | 9.5 | 4.7 |
| Biesenbach, 2000<sup>20</sup> | 36.3 | NR | 60 | 2250 | 50 | 0 | NR | NR | 10 | NR |
| Ekboim, 2001<sup>21</sup> | DN Microalbuminuria | NR | 62 | 91 | 23 | 45 | 3124 | 4 | 2235 | 45 | NR | NR | NR | 4 | 4 |
| Khoury, 2002<sup>22</sup> | Cr <1 mg/dl | Cr 1–1.5 mg/dl | Cr 1.5> mg/dl | 35.7 | 34.3 | 33.3 | NR | <32 weeks | 7.7 | 16.7 | 44.4 | NR | NR | NR | 15.4 | 5.1 | 12.9 |
| Biesenbach, 2000<sup>20</sup> | Microalbuminuria | NR | NR | NR | NR | NR | NR | NR | 9.7 | 9.7 |
| Rossing, 2002<sup>23</sup> | NR | NR | NR | NR | NR | NR | NR | 9.7 | 9.7 |
| Bagg, 2003<sup>24</sup> | NR | NR | NR | NR | NR | NR | NR | 9.7 | 9.7 |
| Carr, 2006<sup>25</sup> | Above target BP (MAP >100 mmHg) | Below target (MAP <100 mmHg) | 35.1 | 32.8 | <32 weeks | 4.6 | 38.1 | 2520 | 9.1 | 28.6 | NR | NR | NR | 9.1 | 9.5 |
| Nelson, 2006<sup>26</sup> | 2000–2003 | 250 days | 259 days | 62 | 40 | 23 | 0 | 3124 | 45 | 3279 | NR | NR | NR | NR | 4 | 4 |
| Nielsen, 2007<sup>27</sup> | Diabetic nephropathy Microalbuminuria | 258 days | 264 days | 71 | 20 | 14 | 0 | 2765 | 29 | 14 | NR | NR | NR | NR | 0 | 0 |
| Yoge, 2009<sup>28</sup> | Non-complicated pregnancy Complicated pregnancy | 37.8 | 32.4 | 0 | 32 | NR | NR | 2323 | 0 | 57 | 0 | 46 | NR | NR | 0 | 0 |
| Jensen, 2010<sup>29</sup> | Non-complicated pregnancy | 260 days | 36 | 16 | 3335 | NR | 50 | NR | 19 | 5 | NR |
| Bell, 2012<sup>30</sup> | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | Unadjusted OR 2.78 (1.14 to 5.25) Adjusted OR 2.45 (1.15 to 5.25) |
| Young, 2012<sup>31</sup> | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Damm, 2013<sup>32</sup> | Type 2 DN | Type 1 DN | T2 microalbuminuria | T1 microalbuminuria | 250 days | 249 days | 260 days | 259 days | 50 | 40 | 2460 | 40 | 60 | NR | NR | NR |
| Piccoli, 2013<sup>33</sup> | 32.5 | 100 | 58 | 1919 | 7.6 | NR | 85 | 20 | 0 | 9.5% of total cohort |
| Kleinetti, 2015<sup>34</sup> | 1988–1999 group | 2000–2011 group | 254 days | 246 days | 70.8 | 76.7 | <32 weeks | 17.8 | 20.9 | 2978 | 15.4 | 23.3 | 35.4 | 27.9 | 26.2 | 48.8 |
| Seah, 2020<sup>35</sup> | Microalbuminuria group | Macraalbuminuria group | OR 3.9 (1.5 to 9.9) | 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

| Study                              | Follow-up post delivery | Worsening proteinuria | Worsening renal function | Doubling creatinine | Mean eGFR decline/year | ESRF |
|------------------------------------|-------------------------|-----------------------|--------------------------|---------------------|------------------------|------|
| Reece, 1990                        | 29 months               | 27%                   | 27%                      | 9%                  | 0                      | 0    |
| Combs, 1993                        | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Hod, 1995                          | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Kimmerlie, 1995                    | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Gordon, 1996                       | 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% |
| Subgroup <1 g proteinuria and CrCl >90 mL/min | 29 months | 27% | 27% | 9% | 0 | 0 |
| Kaaja, 1996                        | 5–9 years               | 4/6                   | 2/3                      | NR                  | NR                     | 1/6  |
| Mackie, 1996                       | 6 months–8 years        | NR                    | 50% (3)                  | 9% (1)              | NR                     | 50% (3) (9% (1) |
| Miodovnik, 1996                    | 9.5 years               | NR                    | NR                       | NR                  | 8–10 mL/year           | 26% 0.7% |
| Purdy, 1996                        | 35–138 months           | 82%                   | 45%                      | NR                  | NR                     | 6%   |
| Zhu, 1997                          | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Reece, 1998                        | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Bar, 1999                          | 2 years                 | NR                    | 0                        | 0                   | NR                     | Nil  |
| Biesenbach, 1999                   | 6 months                | 2.2 g/24 h to 2.8 g/24 h | No change               | 87%                 | 61 mL/min to 38 mL/min | NR   |
| Dunne, 1999                        | 2                      | NR                    | No difference            | No difference       | NR                     | 5%   |
| Biesenbach, 2000                    | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Ekbom, 2001                        | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Khoury, 2002                       | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Rossing, 2002                      | 10 years                | 534 to 786 mg/24h     | 31%                      | 33%                 | 2.2 mL/min             | 19% 24% |
| Bagg, 2003                         | 6 years                 | NR                    | NR                       | NR                  | NR                     | 36%  |
| Carr, 2006                         | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Nielsen, 2006                      | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Nielsen, 2009                      | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Yogev, 2009                        | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Jensen, 2010                       | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Bell, 2012                         | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Young, 2012                        | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Damm, 2013                         | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Piccoli, 2013                      | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Klemetti, 2015                     | NR                      | NR                    | NR                       | NR                  | NR                     | NR   |
| Seah, 2020                         | 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.
Management of diabetic kidney disease in pregnancy

| Pre-pregnancy | During pregnancy | Post-partum |
|---------------|-----------------|-------------|
| • 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. | • 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. |
| • 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). | • Ensure follow-up with nephrologist post-partum (and with the diabetes services if not already engaged). |
| • 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. | • High dose folate acid 5 mg should be started 3 months prior to conception. |
| • Target blood pressure of 110–130 mmHg (systolic) and 70–90 mmHg (diastolic) should be used. | • Target blood pressure of 110–130 mmHg (systolic) and 70–90 mmHg (diastolic) should be used. | • The HbA1c should be below 48 mmol/mol prior to conception (if achievable without causing problematic hypoglycaemia). |
| • The creatinine and ACR/PCR should be checked at least 4-weekly and at least fortnightly from 32 weeks of gestation. | • The creatinine and ACR/PCR should be checked at least 4-weekly and at least fortnightly from 32 weeks of gestation. | • High dose folate acid 5 mg should be started 3 months prior to conception. |

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

Important aspects of management include pre-pregnancy counselling, close multidisciplinary antenatal monitoring with strict blood pressure control, preeclampsia prophylaxis and consideration of thromboprophylaxis and early reintroduction of ACE inhibitors and angiotensin receptor blockade is not advised until breastfeeding cessation. 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.

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