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REVIEW

Type 1 Diabetes, Diabetic Nephropathy, and Pregnancy: A Systematic Review and Meta-Study

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■ Abstract

BACKGROUND: In the last decade, significant improvements have been achieved in maternal-fetal and diabetic care which make pregnancy possible in an increasing number of type 1 diabetic women with end-organ damage. Optimal counseling is important to make the advancements available to the relevant patients and to ensure the safety of mother and child. A systematic review will help to provide a survey of the available methods and to promote optimal counseling. **OBJECTIVES**: To review the literature on diabetic nephropathy and pregnancy in type 1 diabetes. **METHODS**: Medline, Embase, and the Cochrane Library were scanned in November 2012 (MESH, Emtree, and free terms on pregnancy and diabetic nephropathy). Studies were selected that report on pregnancy outcomes in type 1 diabetic patients with diabetic nephropathy in 1980-2012 (i.e. since the detection of microalbuminuria). Case reports with less than 5 cases and reports on kidney grafts were excluded. Paper selection and data extraction were performed in duplicate and matched for consistency. As the relevant reports were highly heterogeneous, we decided to perform a narrative review, with discussions oriented towards the period of publication. **RESULTS**: Of the 1058 references considered, 34 fulfilled the selection criteria, and one was added from reference lists. The number of cases considered in the reports, which generally involved single-center studies, ranged from 5 to 311. The following issues were significant: (*i*) the evidence is scattered over many reports of differing format and involving small series (only 2 included over 100 patients), (*ii*) definitions are non-homogeneous, (*iii*) risks for pregnancy-related adverse events are increased (preterm delivery, caesarean section, perinatal death, and stillbirth) and do not substantially change over time, except for stillbirth (from over 10% to about 5%), (*iv*) the increase in risks with nephropathy progression needs confirmation in large homogeneous series, (*v*) the newly reported increase in malformations in diabetic nephropathy underlines the need for further studies. **CONCLUSIONS**: The heterogeneous evidence from studies on diabetic nephropathy in pregnancy emphasizes the need for further perspective studies on this issue.

Keywords: type 1 diabetes · nephropathy · pregnancy · preeclampsia · chronic kidney disease · preterm delivery

Background

Diabetic nephropathy is the main cause of end-stage kidney disease worldwide [1-3]. Despite major improvements in diabetic care, its overall incidence remains considerable, and it is increasing in type 2 diabetes because of life span prolongation in diabetic patients among other factors [1-4]. While both the presentation and onset of diabetic nephropathy in type 1 diabetes have changed over time in developed countries, with delayed onset and a reduced number of cases

with nephrotic syndrome, the prognosis in developing countries is still poor. The increase in patients with suboptimal diabetes control and the presence of severe diabetic nephropathy in young type 1 patients present a challenge to both nephrologists and obstetricians [5-7].

The prevalence of type 1 diabetes during pregnancy is variable world-wide and there are differences in the definition of diabetic nephropathy [8-9], which makes it difficult to combine epidemiological data. When diabetic nephropathy is broadly defined as the presence of any sign of renal disease including microalbuminuria, its prevalence ranges from 5% to over 25% in type 1 diabetic pregnant women. The highest prevalence is recorded in tertiary care centers owing to the obvious selection of referred patients [10-12].

Diabetes during pregnancy has been associated with a variety of complications, including congenital malformations, fetal growth retardation, stillbirth, early mortality, and preterm delivery [13-18]. In this context, the presence of diabetic nephropathy adds further risks. These include progression of chronic kidney disease during or after pregnancy, worsening of microvascular or macrovascular disease and increased incidence of pregnancy-related hypertensive disorders such as pregnancy-induced hypertension, pre-eclampsia (PE) or HELLP syndrome [19-24]. The definition of hypertensive disorders may be challenging since PE features (proteinuria and hypertension after the 20th gestational week) overlap with those of diabetic nephropathy. Moreover, definitions of "superimposed PE" are non-univocal [25-26].

The improvements in maternal-fetal care and the increased recognition of the effects of kidney disease in pregnancy have contributed to significant changes in the risk-benefit balance of "high risk" pregnancies and changed the prognosis for preterm babies [31-33]. Furthermore, epigenetic and developmental studies have underlined the importance of early exposure to pathologic noxae in the development of adult diseases, thus raising long-term concerns about preterm, growth-restricted babies and children born of mothers affected by different disorders [34-39].

Despite the fact that there are several recent reviews on the changing clinical spectrum of diabetic nephropathy, no review has analyzed the outcomes of pregnancy in patients with diabetic nephropathy in type 1 diabetes [27-30]. The main reason for performing the present systematic review is the need for constantly updated, evidence-based information for counseling, a pivotal task in the era of patient empowerment [40-41].

Abbreviations:
DCCT - Diabetes Control and Complications Trial
GFR - glomerular filtration rate
HELLP - hemolysis elevated liver enzymes, low platelet
IUGR - intrauterine growth restriction
KDOQI - Kidney Disease Outcomes Quality Initiative
MESH - medical subject headings
NICU - Neonatal Intensive Care Unit
PE - pre-eclampsia
SGA - small for gestational age
SPSS - statistical package for social sciences

Methods

Search strategy

Simultaneous searches were performed in Pubmed, Embase and the Cochrane Library (in the last week of November 2012). The search was deliberately broad to increase sensitivity, according to the guidelines of the Cochrane Collaboration. Search terms included pregnancy as MESH, Emtree and free term and diabetic nephropathy as MESH and free term. The reference lists of reviews and selected papers were also searched for papers that had not been retrieved by the previous search strategy.

Selection criteria

Case series with less than 5 patients and patients with kidney or pancreas-kidney transplant were excluded. Likewise, papers dealing with long-term effects on mother and offspring (over 6 months) were not considered for the present analysis which is limited to pregnancy-related outcomes.

The limitations imposed on the selection of papers related both to patients and to time of publication (as provided by Medline). The period from 1980 to 2012 was selected because of the profound changes in diabetes care that have occurred since the early nineteen-eighties. Although the search was not limited to English, language barriers impaired the evaluation of four papers published in Japanese [42-45].

The search was performed in duplicate by GBP and RC. They worked independently and subsequently matched results. Abstracts and titles were screened by GBP, RC, and GC; controversies were resolved by discussion. The final paper selection was approved by the whole group and data were extracted in duplicate. The study group "Rene e Gravidanza" monitored the retrieved data and the final results.

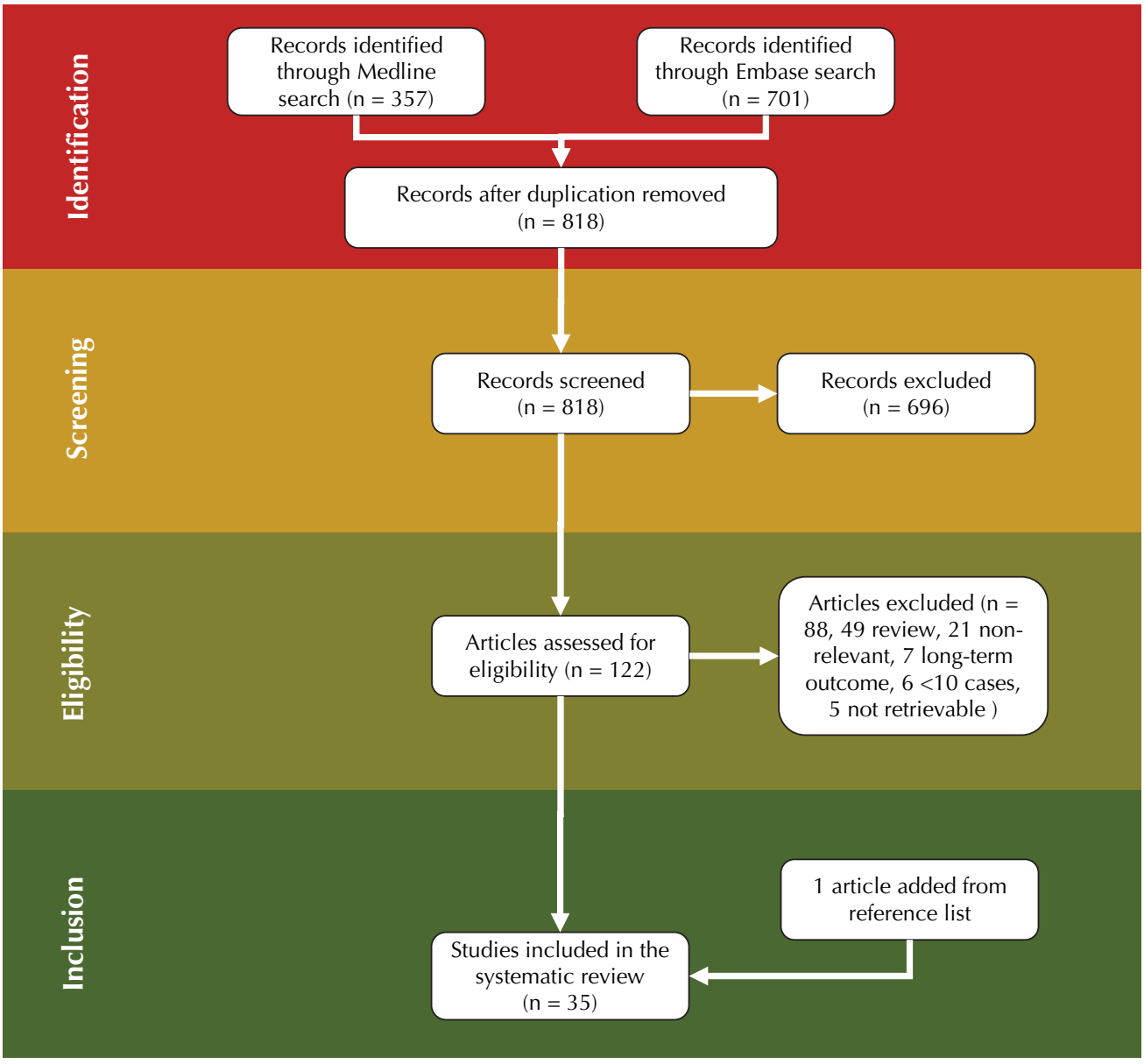

Figure 1. Study design. In total, 818 articles have been retrieved from database screening. After removal of duplicate and non-relevant articles, 122 have been assessed for eligibility. Of these 122 articles, reviews and further non-relevant articles have been excluded such that finally 35 studies could be included in the present study.

Data collection and analysis

The following data were collected: title, author, objective, year, journal, period of study, study centers, country, type of study, number of cases, control group (when present), maternal age, parity, hypertension, PE, proteinuria, glycemic control, drugs, additional care, gestational age, birth weight, indication for delivery, preterm delivery, stillbirth/neonatal death, small for gestational age (SGA), intrauterine growth restriction (IUGR), admission to intensive care unit (NICU), malformations, other neonatal complications (whenever reported), maternal and fetal follow-up, definition of diabetic nephropathy, and inclusion criteria.

Papers were divided into three major periods: 1980-1989; 1990-1999 and 2000 to present. As the definition of PE has changed over time, the older

Table 1. General data on selected studies from 2000-2012

Reference	Period	Country	Main objective (pregnancy in type 1 diabetic mothers)	n	Ctrls
Bell, 2012 [79]	1996-2008	UK	To quantify the risk of congenital anomalies and the influence of peri-conception HbA1c and other clinical and socio-demographic factors	57[a]	1257[b,c]
Themeli, 2012 [78]	NR	Albania	To determine the influence of microalbuminuria on fetal outcome and maternal complications in type 1 diabetes	26	54[c]
Young, 2011 [77]	2010-2011	Brazil	To evaluate the child-bearing effect of pregnancy on DN and of DN on outcomes	11	32[c]
Yogev, 2010 [76]	2000-2007	Israel	To identify risk factors associated with complicated pregnancy in type 1 patients with DN	46	/
Jensen, 2010 [75]	1993-1999	Denmark	To study the association between microalbuminuria, PE and preterm delivery in type 1 diabetes	84	762[c]
Nielsen, 2009 [74]	2004-2006	Denmark	To describe outcomes in normo- microalbuminuria or DN after intensified anti-hypertensive therapy	17	100[c]
Carr, 2006 [73]	1986-2002	USA	To assess the relation between hypertension in early pregnancy and perinatal outcomes in DN	43	/
How, 2004 [72]	NR	USA	To test whether early-pregnancy proteinuria is associated with PE in pregestational diabetes	194[d]	/
Irfan, 2004 [71]	1997-2003	Pakistan	To assess the effect of pregnancy on the course of renal function in patients with DN and retinopathy	35	35[c, g]
Bagg, 2003 [70]	1985-2000	NZ	To assess long-term maternal outcome after pregnancy in women with DN	24[f]	/
Rossing, 2002 [69]	1970-2000	Denmark	To evaluate the long-term impact of pregnancy on the progression of DN	26	67[g]
Khouri, 2002 [68]	NR	USA	To assess the association of renal function with maternal and fetal outcome in DN	72[h]	/
Ekbom, 2001 [67]	1996-2000	Denmark	To determine the influence of microalbuminuria on pregnancy outcome in type 1 diabetes	37	203[c]
Sobczak, 2000 [66]	1991-1999	Poland	To assess the influence of pregnancy on DN	21	233[c]
Biesenbach, 2000 [65]	1985-1993	Austria	To evaluate perinatal complications and follow-up of infants of mothers with DN stage IV	10	30[c]
Schröder, 2000 [64]	NR	Germany	To evaluate the role of stage III diabetic nephropathy on hypertensive pregnancy complications in insulin-treated diabetes	16[i]	86[c]

Legend: [a] 3 cases with type 2 diabetes were not considered. [b] The study reports on 1314 pregnancies in type 1 diabetes, 363 in type 2 diabetes. [c] Pregnant type 1 diabetic patients without nephropathy. [d] Cases: 94 with proteinuria <190 mg/24 h, 35 proteinuria 190-499 mg/24 h, 65 proteinuria >499 mg/24 h. [e] Controls are mentioned, data are not supplied. [f] 14 women. [g] Non-pregnant women with diabetic nephropathy. [h] 58 women. [i] Cases: 8 type 1 diabetes with UAE 30-300 mg/day, 5 gestational diabetes with UAE 30-300 mg/day, 3 with UAE > 300 mg/day. *Abbreviations*: Ctrls – controls, DN – diabetic nephropathy, IDDM – insulin-dependent diabetes mellitus, n – number of pregnancies, NR – not reported, PE – pre-eclampsia, Pro – prospective, Pts – patients, Ret – retrospective. References [64-79].

term "gestosis" was considered equivalent to PE. Relevant definitions (for example as for HELLP or pregnancy-induced hypertension) were also collected.

The decision to perform a narrative or meta-analytical systematic review was dependent on the type and quality of the evidence retrieved. Since we were expecting to deal with a high degree of heterogeneity, a descriptive narrative review was planned for the main results and outcomes, while data pooling was envisaged for each period according to the degree of diabetic nephropathy. Data analysis was performed using SPSS version 18.0.

Results

Retrieving the evidence and summary data

Our search on diabetic nephropathy (type 1 diabetes) and pregnancy identified 209 articles from 1058 references. Thirty-four satisfied the selection criteria, one article was added from the reference lists (**Figure 1**) [12, 46-79]. Sixteen studies (719 pregnancies) published in 2000-2012 (**Table 1**), 15 studies (719 pregnancies) published in 1990-1999 (**Table 2**), and 4 studies (73 pregnancies) published in 1980-1989 were selected (**Table 3**).

Table 2. General data on selected studies from 1990-1999

Reference	Period	Country	Main objective (pregnancy in type 1 diabetic mothers)	n	Ctrls
Biesenbach, 1999 [63]	1982-1996	Austria	To evaluate the influence of pregnancy on renal function in diabetic women with overt DN	14[l]	/
Dunne, 1999 [62]	1990-1997	UK	To determine the effect of DN on maternal and fetal outcome and creatinine variation	21[m]	/
Bar, 1999 [61]	1990-1995	Israel	To examine the effect of pre-pregnancy captopril on renal function and on fetal-maternal outcome in DN	24	/
Bar, 1999 [60]	1990-1995	Israel	To calculate the probability of successful maternal and fetal outcome in patients with underlying renal disease	24	88[n]
Czajkowski, 1999 [59]	NR	Poland	To analyze pregnancy, labor and neonatal complications in DN and proliferative retinopathy	44	/
Reece, 1998 [58]	1980-1990	USA	To evaluate maternal-fetal outcomes in pregnancies complicated by DN	27	/
Purdy, 1996 [57]	1981-1993	USA	To assess the effect of pregnancy on renal function in moderate-to-severe renal insufficiency secondary to DN	14[o]	11[g]
Mackie, 1996 [56]	1985-1993	UK	To examine the effect of pregnancy on maternal renal function in women with DN (moderate vs early)	19[p]	/
Miodovnik, 1996 [55]	1978-1991	USA	To determine whether pregnancy alters the natural course of DN in women with IDDM	46	136[q]
Gordon, 1996 [54]	1988-1994	USA	To evaluate perinatal morbidity and mortality, maternal outcome, and follow-up in DN	46[r]	/
Hopp, 1995 [53]	1980-1990	Germany	To determine the risk factors for maternal and fetal morbidity in patients with diabetic retinopathy and/or DN	76[s]	85[z]
Hod, 1995 [52]	1990-1993	Israel	To examine the effect of pre-pregnancy captopril on renal function and on fetal-maternal outcome in DN	8	/
Kimmerle, 1995 [51]	1982-1993	Germany	To study the effect of DN on pregnancy perinatal outcome, infant development and long-term function	40[t]	110[u]
Combs, 1993 [50]	1982-1991	USA	To assess the relation between proteinuria in early pregnancy and PE in diabetic mothers	311[v]	/
Biesenbach, 1992 [49]	1982-1987	Austria	To study the influence of pregnancy on progression of renal disease in women with IDDM and impaired renal function	5	/

Legend: [g] Non-pregnant women with diabetic nephropathy. [l] 12 women. [m] 18 women. [n] 65 women: 38 with primary renal disease, 27 with functioning renal allograft. [o] 11 women. [p] 17 women. [q] 13 women developed diabetic nephropathy. [r] 45 women. [s] Retinopathy or nephropathy. [t] 33 women. [u] 91 women. [v] 190 proteinuria < 190 mg/day, 45 proteinuria 190-499 mg/day, 62 proteinuria >= 500 mg/day. [z] Patients without severe microangiopathy (White C D). *Abbreviations*: Ctrls – controls, DN – diabetic nephropathy, IDDM – insulin-dependent diabetes mellitus, n – number of pregnancies, NR – not reported, PE – pre-eclampsia, Pro – prospective, Pts – patients, Ret - retrospective. References [49-63].

Most studies were monocentric. Because case reports were not included, the number of observed patients ranged from 5 to 311. Two studies only included more than 100 pregnancies and stratified the patients according to albuminuria levels.

The studies originated from all over the world: ten were from North America, eighteen from Europe, one from Asia, one from New Zealand, one from South America and four from Israel. Overall, Europe and USA are the main sources of the data. The studies were heterogeneous with regard to duration (from 1 to over 20 years) and period of study (1966-1981 through 2010-2011) (**Tables 1-3**). Seventeen studies included "controls". Of these studies, nine included type 1 pregnant diabetic patients without nephropathy as controls.

Definitions and staging of diabetic nephropathy

Most of the studies gave the definition of diabetic nephropathy or the selection criteria employed when they dealt with retrospective analyses (**Tables 4-6**, in the Appendix). However, the defi-

Table 3. General data on selected studies from 1980-1989

Reference	Period	Country	Main objective (pregnancy in type 1 diabetic mothers)	n	Ctrls
Biesenbach, 1989 [48]	1988-1989	Austria	To assess the relation between microalbuminuria and changes in proteinuria and kidney function during and after pregnancy and the incidence of transient nephrotic syndrome in pregnancy	7	7[c]
Reece, 1988 [12]	1975-1984	USA	To assess the effects of diabetes-associated renal disease on maternal and neonatal outcomes in pregnancy and follow-up	31	/
Biesenbach, 1987 [47]	NR	Austria	To assess the relation between stage of DN and changes in proteinuria and renal function during and after pregnancy	9	/
Kitzmiller, 1981 [46]	1975-1978	USA	To assess the effects of DN on pregnancy, perinatal outcome and infant development and the influence of pregnancy on maternal hypertension and renal function	26	/

Legend: [c] pregnant type 1 diabetic patients without nephropathy. *Abbreviations*: DN – diabetic nephropathy, NR – not reported. References [12, 46-48].

nitions differed over time. Diabetic nephropathy was more often defined by albumin excretion rates. The cut-off point most frequently applied since 2000 was 300 mg/day, while 500 mg/day was generally used before that date. Some studies included serum creatinine in the definition (e.g. Yogev, 2010 [76]), while others stressed the fact that urinary albumin excretion (UAE) should be considered when bacteriuria and other signs of kidney disease (e.g. Biesenbach, 1999 [63]) are absent or diabetic retinopathy (e.g. Bagg, 2003 [70]) or hypertension (i.e. Schröder, 2000 [64]) are present.

Microalbuminuria represents a "huge area", occasionally defined as "non-apparent diabetic nephropathy" (Schröder, 2000 [64]) or included in "diabetic nephropathy" (Young, 2011 [77]) (**Tables 4-6**, in the Appendix). In line with the changes in age at conception observed in the last decades, mean/median age has progressively increased in Western countries from the 20s to the 30s, in particular over the periods of 1980-1990 and 2010-2013. This may reflect a delay in the onset of diabetic nephropathy (**Tables 4-6**, in the Appendix).

Diabetes control, reported at different intervals during pregnancy, is also variable as a reflection of study settings and patient selection (**Tables 4-6**, in the Appendix).

Main maternal outcomes

Main maternal outcomes are reported in **Tables 7-9** (in the Appendix). According to the search strategy, papers containing information on short-term pregnancy-related outcomes were included in the analysis. Five papers were mainly dealing with long-term outcomes, but also included short-term data, and were thus selected as well.

Proteinuria and hypertension are the main hallmarks of diabetic nephropathy during pregnancy. Pre-eclampsia is usually defined as proteinuria >300 mg/day, hypertension in the absence of proteinuria and pre-conception hypertension. However, the role of baseline microalbuminuria is not clear and none of the studies give any information on uteroplacental blood flows or other obstetrical or biochemical markers of PE (**Tables 7-9**, in the Appendix). The different definitions of PE may account for some of the differences recorded. PE and/or nephrotic proteinuria, considered together, are described in over 60% of cases with baseline nephropathy (for example Themeli 2012 [78], Young 2011 [77], Ekbom 2001 [67], Biesenbach 1999 [63] and 2000 [65]). In the few papers reporting on this medium-term outcome, proteinuria slowly decreases towards baseline in 3-6 months (Biesenbach 1999 [63], Biesenbach 1992 [49], Kitzmiller 1981 [46]) (**Tables 7-9**, in the Appendix).

Regarding the parameters of renal function, the wide variety of definitions and patient selection criteria did not allow data pooling. All possible outcomes are reported:

1. Physiological increase in glomerular filtration rate (GFR) throughout pregnancy (Young 2011 [77])
2. Stable kidney function (Bar 1999 [61])
3. Individual patterns (Mackie 1996 [56], Reece 1988 [12])
4. Frequent worsening (Biesenbach 1999 [63], Biesenbach 2000 [65], Rossing 2002 [69])

In those papers describing different stages of diabetic nephropathy, worsening is reported as

more frequent in cases where there is functional impairment or severe proteinuria at baseline (**Tables 7-9**, in the Appendix). However, the inhomogeneity of the definitions prevents the pooling of data. In the context of good overall glycemic control, no clear link between glycated hemoglobin and outcomes would appear to be evident in this descriptive analysis.

Notably, maternal age reported in the papers showed an increasing trend, presumably in parallel to the increase in the overall population. All the series published in the first decade include women younger than 30 years (mean or median age). In the second decade, women aged less than 30 years make up 11/15 of the patients (7 <28 years) and this figure is 10/16 in the last period (2000-2012). In the last period, 2 series only include cases with a mean/median age <28 years.

Main fetal outcomes

The main fetal outcomes are reported in **Tables 10-12** (in the Appendix). No paper reported control data in "normal", non-diabetic pregnancies. Interestingly, when the three papers (Themeli 2012 [78]; Nielsen 2009 [74]; Ekbom 2001 [67]) which use non-microalbuminemic patients, homogeneously defined, as controls are considered, a higher prevalence of adverse pregnancy-related events in cases with micro- and macro-albuminuria is confirmed as is also the case for SGA and preterm delivery (both at gestational age <34 and <37 weeks), although the prevalence of perinatal death and stillbirth is not higher, possibly because of the small number of cases (**Table 13**).

Caesarian section rates in microalbuminuric patients vary widely from none (Nielsen, 2009 {74]) to about 20%. Higher levels are recorded in patients with full-blown diabetic nephropathy (up to over 90% according to Khouri 2002 [68]). The incidence of preterm delivery is likewise high, within a wide range, and it is almost the rule in full-blown diabetic nephropathy. Again, there is an increasing trend in severe diseases (albeit differently defined) (**Tables 10-12**, in the Appendix).

Against a background of risk for macrosomal babies, the incidence of SGA and IUGR increased along with worsening of kidney disease. Once more, the definitions of SGA and IUGR were nonunivocal and this may account for at least part of the reported variability (**Tables 10-12**, in the Appendix). As a reflection of the different definitions and populations studied, the prevalence of preterm delivery remained high without a decreasing trend over the three decades analyzed.

It is worth noting that the incidence of stillbirth and neonatal death has remained high in recent years (5.5% according to Themeli 2012 [78], 6% according to Yogev 2010 [76]). However, there may be suggestions of an improving trend as compared with the cumulative incidence of neonatal and fetal death of over 10% in the eighties. The inhomogeneity of the definitions prevents further pooling of the data. In the context of overall good glycemic control, no clear link between glycated hemoglobin and outcomes would appear to be evident in this descriptive analysis. Only one paper specifically reported on malformations, described as increased in diabetic nephropathy as compared with diabetic patients (Bell, 2012 [78]).

Discussion

The most common complications of diabetes and pregnancy affect the kidney. It is not surprising therefore that several pregnancy-related adverse outcomes, such as hypertension, proteinuria and PE, were more common in diabetic patients, and even more common in patients with diabetes and kidney disease [10-17].

In an era when patients are increasingly required to participate in therapeutic choices, a systematic review of the literature may be helpful for counseling. Thus, the present review started from the early eighties, the time when the DCCT study set new standards and goals for diabetic care [80]. The review deals with short-term pregnancy-related outcomes, by definition within 6 months of delivery or after birth.

In our opinion, five major points emerge from our analysis which are potentially relevant to patient counseling. The first point is the relatively limited evidence available on this very important and challenging nephropathy (**Tables 1-3**). In fact, out of thirty-four papers retrieved, only two reported on more than 100 patients, while most studies (28/35) described less than fifty patients (**Tables 1-2**). The second point relates to the definitions of diabetic nephropathy. In fact, after the publication of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, attention shifted to earlier stages of kidney disease, in part as a reflection of the change in the definition of chronic kidney disease, which was substantially modified in the new millennium [81] (**Tables 4-6**, in the Appendix). In diabetic nephropathy, as well as in clinical nephrology, a common language is urgently required [26]. The wide range of definitions of diabetic nephropathy is likely to affect the results. In recent reports, diabetic nephropathy has in-

cluded albuminuria or required urinary proteins to reach 0.5 g/day. It may or may not take serum creatinine into account or require the presence of other signs of microvascular disease (**Tables 4-6**, in the Appendix).

These first two points should give rise to discussion of the limits and biases of the available evidence in the context of patient counseling. Given these limits, the third point is that, in each period of study, there was substantial agreement on a negative observation. Indeed, the risks for pregnancy-related adverse events were increased in patients with type 1 diabetes and diabetic nephropathy (**Tables 1-12**).

Furthermore, there would appear to be an overall increase in risk as diabetic nephropathy progresses, following a trend similar to that observed in other kidney disease [26, 82, 83]. Maternal outcomes are widely scattered and probably reflect several factors: the lack of univocal definitions of diabetic nephropathy, chronic kidney disease, and PE, increasing maternal age over time, different study aims, patient selection and the setting of several studies, small sample size, and single-center and care setting (**Tables 1-12**).

Within this framework, two further aspects may be emphasized. The risks do not decrease over time (**Tables 7-9**, in the Appendix). An increase in maternal age, observed over time, and presumably paralleling the ageing of the overall population, may be one of the clues which explains part of this phenomenon, as an increase in maternal age is associated with an independent risk for adverse pregnancy-related outcomes and proteinuria. Hypertension, proteinuria and PE are the most relevant challenges; however the relative role of each complication is difficult to determine, another reflection of the non-univocal definition of PE and "superimposed PE", in particular with respect to microalbuminuria (**Tables 7-9**, in the Appendix). In fact, the strict definition of PE (proteinuria and hypertension after the 20th gestational week in a previously normotensive, non proteinuric patient), was designed to identify cases without kidney damage at baseline, a situation that hardly applies to patients with microvascular disease [25].

Conversely, the risks of a worsening in kidney function are more difficult to summarize, as all possible occurrences are reported in the studies (increase, decrease, stable kidney function) and probably depend upon a complex interaction between baseline function and pregnancy-related outcomes. Furthermore, without a comparison of long-term outcomes in type 1 diabetic patients with a comparable degree of kidney disease but no pregnancies it is impossible to reach definitive conclusions (**Tables 4-9**, in the Appendix). Thus, counseling on the maternal risks should underline the increased risk of developing hypertension and proteinuria, either in the context of PE or as a specific response of baseline nephropathy to the challenge presented by hyperfiltration during pregnancy. Moreover, it is important to mention the highly unpredictable but observed risk of a worsening in kidney function during pregnancy and after delivery (**Tables 7-9**, in the Appendix). Remarkable differences in the reported outcomes suggested a relevant "center effect" and they are in favor of referral to experienced settings.

The last two points concern fetal outcomes. The first is related to the greatest risks of diabetic pregnancies: stillbirth or fetal death (**Tables 10-12**, in the Appendix). While the high risk of prematurity and SGA or intrauterine growth restriction is also shared by patients with other kidney disorders and increases as the kidney disease progresses, stillbirth or fetal death are shared only by patients with systemic lupus erythematous, another systemic syndrome with remarkable microvascular damage [26, 82, 83]. The risk has also been reported in diabetic patients without overt nephropathy, but appears to be increased in the setting of diabetic nephropathy (**Tables 10-12**, in the Appendix). Interestingly, even if the risks of stillbirth and fetal death have been reduced in the period from 2000 to date compared to the eighties (from over 10% to about 5%), the reduction is much less than that observed in the case of mothers on dialysis for example, which has decreased by 25% in each decade since the eighties, albeit starting from a much higher level [84-86]).

The last issue touches on a very specific point: the increase in fetal malformations in diabetic nephropathy, as compared with diabetes, reported in a single recent paper [79]. The study in question, which challenges an old theory stating that the presence of kidney disease may complicate the clinical management of pregnancy but does not increase the risk of malformations, will need further confirmation. It also emphasized how much has to be studied in the field of diabetic nephropathy and pregnancy.

The limitations of systematic reviews are primarily the limitations of the current evidences. Our study therefore reflected the lack of large control groups and the high heterogeneity of the selected papers. Furthermore, as we chose to give a wide panorama of the current evidence; we did not limit our selection to the few papers with control groups or shared definitions of PE or diabetic

nephropathy, thus preferring a narrative over a meta-analytical approach.

Several suggestions for future research may arise from the limits of the present review. First of all, the data available mainly reflect the European and USA standards of care, and only a few papers, in the recent period, came from developing countries (Pakistan, Brazil, **Tables 1-3**). We are acutely aware of the differences in general health status and medical practice of different populations and hope that our study may revive interest and awareness resulting in the collection of more information that can be used to tailor dedicated approaches. Ideally, future papers should include homogeneous information not only on the main maternal-fetal outcomes, homogeneously defined, but also on other outcome modifiers including the following type of care (multidisciplinary versus mainly managed in the nephrology or diabetology setting), adherence to the current guidelines (specifying the guideline in question), concurrent diabetes-related comorbidity with particular emphasis on retinopathy (as a marker of microvascular disease) and obesity and cardiovascular disease with information on their independent effect on pregnancy-related outcomes.

Within these limits, our study represents the only available systematic review recently undertaken on diabetic nephropathy in pregnancy. It may be of use both in counseling, when it is important to emphasize the limits of the current evidence, and in planning future research, which is urgently needed to reduce the adverse outcomes associated with this ancient and yet mysterious disease.

Conclusions

In conclusion, evidence on diabetic nephropathy in type 1 diabetic patients during pregnancy was plentiful albeit non-homogeneous. Despite great advances in maternal-fetal care and in diabetes control, the risks for the major adverse maternal-fetal outcomes have not substantially decreased over time.

Subtle changes in the populations studied may partly account for this unexpected result. The data underline the need for prospective, multicenter studies, with clearly defined outcomes and data collections, which would not only promote better understanding, but also assist in producing and updating practical algorithms on the care of pregnant women with diabetic nephropathy.

In any case, our review underlines the need for further studies to obtain better insight into the complex relationship between pre-existing and pregnancy-induced microvascular damage and the need for careful, multidisciplinary counseling, with particular attention to the uncertainties and limits of the currently available evidence.

Author contributions: GBP designed the study. GBP, RC, and MF drafted the manuscript. AR and TT participated in the writing of the final version of the manuscript. NC, GM, and NC retrieved the evidence and controlled the searches. RC and GBP selected the papers. SG, ET, EM, and CM extracted the data and drafted the tables. GC and GG monitored the data and double-checked all retrieved papers.

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■ Appendix

Table 4. Main definitions of diabetic nephropathy in type 1 diabetes, diabetes control, and subgroups considered from 2000-2012

Reference	Main definitions of diabetic nephropathy	Subgroups (n)	HbA1c (%) conception	Maternal age
Bell, 2012 [79]	NR	Type 1 diabetes (I): 1314 Type 2 diabetes (II): 363	I: 8.1 II: 7.0	I: 29 (24-33) II: 33 (29-37)
Themeli, 2012 [78]	Proteinuria >300 mg/day	Controls (I): 54 Microalbuminuria (II): 18 Diabetic nephropathy (III): 8	2-6 w: I: 7.2±1.4 II: 8.0±1.1 III: 9.0±1.4	I: 28±5 II: 30±3 III: 30±4
Young, 2011 [77]	UAE ≥30 mg/day	No nephropathy (I): 32 Nephropathy (II): 11	I: 7.75 II: 8.5	I: 28 (18-41) II: 28 (21-32)
Yogev, 2010 [76]	Proteinuria ≥300 mg/day before conception or in the 1st trimester or sCr >1.5 mg/dl	No complications (I): 15 Complications (II): 31	I: 7.1±1.5 II: 7.5±1.8	I: 31.8±4.5 II: 31.2±4.6
Jensen, 2010 [75]	Overt DM: UAE ≥300 mg/day or 200 ug/min; micro-albuminuria: 30-300 mg/day pre and/or 1st trimester	Controls (I): 762 Microalbuminuria (II): 84	1st trim.: I: 7.1 II: 7.6	I: 28 (25-32) II: 27 (24-31)
Nielsen, 2009 [74]	UAE ≥300 mg/day; microalbuminuria: UAE 30-299 mg/day	Normoalbuminuria (I): 100 Microalbuminuria (II): 10 Nephropathy (III): 7	I: 6.7 II: 6.9 III: 6.5	I: 30.5 (21-42) II: 31 (21-34) III: 30 (23-39)
Carr, 2006 [73]	Urinary protein ≥300 mg/day pre or first half of pregnancy; renal insufficiency: sCr >1.2 mg/dl or CCr <90 ml/min	MAP < 100 mmHg (I): 22 MAP ≥ 100 mmHg (II): 21	1st trim: I:8.1±0.4 II: 8.0±0.3	I: 29.5±1 II: 27.2±1.2
How, 2004 [72]	NR	Proteinuria <190 mg/day (I): 94 190-499 (II): 35 >499 (III): 65	NR	I: 24.8±5.7 II: 26.2±6.8 III: 25.3±5.3
Irfan, 2004 [71]	Moderate-severe RD: sCr ≥1.4 mg/dl; increase: sCr ≥50% over baseline or 2-fold increase (1/sCr over time)	-	8.7	29.2±5
Bagg, 2003 [70]	Retinopathy + albuminuria (>300 mg/day)	-	NR	30 (19-47)
Rossing, 2002 [69]	Persistent albuminuria >300 mg/day in 2/3 consecutive 24-h urine, retinopathy and no other kidney disease	Non-pregnant (I): 67 pregnant (II): 26	NR	I: 27 II: 24
Khouri, 2002 [68]	Total urinary protein excretion > 500 mg/day in the absence of bacteriuria	sCr ≤1 mg/dl (I): 49 sCr 1-1.5 mg/dl (II): 13 sCr >1.5 mg/dl (III): 10	1st trim: I: 9.9±2.5 II: 9.5±1.9 III: 8.9±0.67	I: 26.3±4.9 II: 28.3±4.1 III: 29.0±4.4
Ekbom, 2001 [67]	Microalbuminuria: 30-300 mg/day; nephropathy: >300 mg/day	Normoalbuminuria (I): 203 Microalbuminuria (II): 26 Nephropathy (III): 11	2-6 w:I: 7.5±1.1 II: 8.1±0.9 III: 8.8±1.3	I: 30±4 II: 29±4 III: 30±3
Sobczak, 2000 [66]	UAE > 500 mg/day	Nephropathy (I): 21 No nephropathy (II): 233	NR	I: 29.3±5.26 II: 28.4±6.15
Biesenbach, 2000 [65]	Preconceptional macroproteinuria (>500 mg/day) without UTI/other renal diseases	Nephropathy (I): 10 No nephropathy (II): 30	NR	I: 28±3 II: 25±3
Schroder, 2000 [64]	Non-apparent diabetic nephropathy: UAE 30-300 mg/day; overt nephropathy: with high BP	UAE > 30 mg/day (I): 10 BP ≥ 140/90 mmHg (II): 7 Other (III): 85	In pregnancy: I: 4.7 II: 5.2 III: 5.1	29 (18-42)[a]

Legend: [a] without any subgroup specification. [b] value as SD above mean. [c] White class B: onset at age 20 or older or duration < 10 years; class C: onset at age 10-19 or duration 10-19 years; class D: onset < 10 or duration > 20 years; class E: overt diabetes mellitus with calcified pelvic vessels; class F: diabetic nephropathy; class R: proliferative retinopathy; class RF: retinopathy and nephropathy; class H: ischemic heart disease; class T: prior kidney transplant. *Abbreviations*: PE – preeclampsia, SBP – systolic blood pressure, DBP – diastolic blood pressure, µg – microgram, sCR – serum creatinine, CCr – creatinine clearance rate, MAP – mean arterial pressure, UAE – urinary albumin excretion, ESRD – end-stage renal disease. ACOG – American College of Obstetricians and Gynecologists, AKF – acute kidney failure, PtU – proteinuria, wk – week, trim – trimester, DN - diabetic nephropathy, NR – not reported, HbA1c – glycated hemoglobin. References [64-79].

Table 5. Main definitions of diabetic nephropathy in type 1 diabetes, diabetes control, and subgroups considered from 1990-1999

Reference	Main definitions of diabetic nephropathy	Subgroups (n)	HbA1c (%) conception	Maternal age
Biesenbach, 1999 [63]	Macroproteinuria (>500 mg/day), normal urine sediment, normal-sized kidneys, proliferative retinopathy	Normal CCr increase (I): 5 Abnormal CCr profile (II): 7	I: 8.0±1.3 II: 8.0±0.9	I: 28±3 II: 29±3
Dunne, 1999 [62]	Mild RD: sCr <100 umol/l; moderate: sCr 101-150 umol/l; severe: sCr >151 umol/l; low grade proteinuria: 300-3000 mg/day; high grade: > 3000 mg/day	Mild nephropathy (I): 17 Moderate (II): 3 Severe (III): 1	6-12 weeks: 9.7 (6.7-16.7)[a]	26.5 (21-40)[a]
Bar, 1999 [61]	Proteinuria >500 mg/day; mild RD: sCr <1.4 mg/dl; moderate: sCr 1.4-2.4 mg/dl; severe: sCr >2.5 mg/dl; PtU grade 1: 20-300 mg/day; 2: 300-3000 mg/day; 3: >3 g/day	-	7.9±0.2	26±2.9
Bar, 1999 [60]	As Bar 1999	Primary renal disease (I): 38 Diabetic nephropathy (II): 24 Renal allograft (III): 27	NR	I: 30±4.9 II: 26±2.9 III: 29±3.6
Czajkowski, 1999 [59]	According to White classification[c]	White class R (I): 14; class F (II): 3 Class FR (III): 19; class T (IV): 2	NR	NR
Reece, 1998 [58]	Macroproteinuria: >300 mg albumin or total protein excretion/day	-	NR	26.6 (21-36)
Purdy 1996 [57]	Moderate-severe RD: sCr ≥1.4 mg/dl; increase: sCr ≥50% over baseline or 2-fold increase (1/sCr over time)	Pregnant (I): 11 Non-pregnant (II): 11	I: 8.7±1.0 II: NR	I: 29.2±5 II: 31.8±8.5
Mackie, 1996 [56]	Pre-pregnancy PtU >500 mg/day; no UTI, hematuria or renal disease, normal kidneys and diabetic retinopathy; moderate RD (pre): sCr 125–250; mild: sCr <125 umol/l	Moderate nephropathy (I): 7 Early nephropathy (II): 12	I: 12.6 II: 10.6	I: 30.6±4.99 II: NR
Miodovnik, 1996 [55]	Total protein excretion rate ≥500 mg/day or persistent positive albuminuria (dipstick ≥ +2) without bacteriuria	Nephropathy (I): 46 No nephropathy (II): 136 Nephropathy developed (IIa):13 Not developed (IIb): 123	Ia: 3.9±3.5 Ib: 4.0±3.6 IIa: 4.1±2.8 IIb: 3.5±3.1	Ia: 24.4±3.6 Ib: 25.1±4.2 IIa: 26.2±4.0 IIb: 25.0±5.2
Gordon, 1996 [54]	CCr <90 ml/min, proteinuria ≥400 mg/day before 20 weeks' gestation or antenatal >500 mg/day; severely reduced renal function: CCr <60 ml/min	-	NR	25.5±4.4
Hopp, 1995 [53]	Clinical evident nephropathy (White classification)[c]	White class RF (I): 76 Class CD (II): 85	NR	NR
Hod, 1995 [52]	Proteinuria >500 mg/day	-	7.9±0.4	23–29
Kimmerle, 1994 [51]	PtU >400 mg/day or CCr <80 ml/min, hypertension; impaired renal function: CCr 32-77 ml/min or sCr 99-214 umol/l	Nephropathy (I): 36 No nephropathy (II): 110	NR	I: 29±5 II: 28±4
Combs, 1993 [50]	Proteinuria ≥500 mg/day pre-pregnancy or before 20 weeks' gestation	PtU <190 mg/day (I): 190 190-499 mg/day (II): 45 ≥500 mg/day (III): 62	12-16 wk: I: 8.5±1.6 II: 9.0±1.7 III: 9.0±1.9	I: 27.7±5.5 II: 27.8±5.8 III: 27.3±5.4
Biesenbach, 1992 [49]	Sonographically normal kidneys, normal urine sediment, significant proteinuria and retinopathy	-	7.5±0.5	28±8

Legend: [a] without any subgroup specification. [b] value as SD above mean. [c] White class B: onset at age 20 or older or duration < 10 years; class C: onset at age 10-19 or duration 10-19 years; class D: onset < 10 or duration > 20 years; class E: overt diabetes mellitus with calcified pelvic vessels; class F: diabetic nephropathy; class R: proliferative retinopathy; class RF: retinopathy and nephropathy; class H: ischemic heart disease; class T: prior kidney transplant. *Abbreviations*: PE – preeclampsia, SBP – systolic blood pressure, DBP – diastolic blood pressure, µg – microgram, sCR – serum creatinine, CCr – creatinine clearance rate, MAP – mean arterial pressure, UAE – urinary albumin excretion, ESRD – end-stage renal disease. ACOG – American College of Obstetricians and Gynecologists, AKF – acute kidney failure, PtU – proteinuria, wk – week, trim – trimester, DN – diabetic nephropathy, NR – not reported, HbA1c – glycated hemoglobin. References [49-63].

Table 6. Main definitions of diabetic nephropathy in type 1 diabetes, diabetes control, and subgroups considered from 1980-1989

Reference	Main definitions of diabetic nephropathy	Subgroups (n)	HbA1c (%) conception	Maternal age
Biesenbach, 1989 [48]	Microalbuminuria: UAE 30-250 mg/day; macro-proteinuria: >500 mg/day; nephrotic: >3000 mg/day	Microalbuminuria (I): 7 Normoalbuminuria (II): 7	I: 6.8±0.6 II: 6.2±1.1	I: 23±5 II: 22±5
Reece, 1988 [12]	Urinary protein ≥300 mg/day before 3rd trimester without other renal disease	-	NR	28±5.7
Biesenbach, 1987 [47]	Microalbuminuria: UAE 30-300 mg/day; nephropathy: >300 mg/day	Normoalbuminuria (I): 5 Microalbuminuria (II): 6 Proteinuria (III): 3	12 wk: I: 5.4±0.3 II: 6.7±0.6 III: 7.2±0.8	24 (18-32)[a]
Kitzmiller, 1981 [46]	Proteinuria >400 mg/day without UTI	-	NR	27

Legend: NR – not, UAE – urinary albumin excretion, HbA1c – glycated hemoglobin. References [12, 46-48].

Table 7. Main maternal outcomes from 2000-2012

Reference	Subgroups	Hypertension (pregnancy-induced)	Pre-eclampsia	Proteinuria	Kidney function in pregnancy
Bell 2012 [79]	Type I (I) Type II (II)	NR	NR	NR	NR
Themeli 2012 [78]	Ctrl (I) Microalb (II) Nephro (III)	I: 3.7% II: 5.5%	I: 7.4% II: 38.8% III: 62.5%	I: 0% >3000 mg/day II: 27.7% III: 62.5%	NR
Young 2011 [77]	No nephro (I) Nephro (II)	I: 21.9% II: 72.7%	I: 6.3% II: 63.6%	UAE (pre-pregnancy, 3rd trimester): I: 3.15→7.78 mg/day II: 119→592 mg/day	CCr (pre-pregnancy, 3rd trimester): I: 98→ 137 ml/min II: 81 → 110 ml/min
Yogev 2010 [76]	No compl (I) Compl (II)	NR	NR	NR	NR
Jensen 2010 [75]	Ctrl (I) Microalb (II)	2nd trimester: I: 1.5% II: 13%	I: 12% II: 41%	NR	NR
Nielsen 2009 [74]	Normoalb (I) Microalb (II) Nephro (III)	I: 120/72 mmHg II: 122/75mmHg III: 135/74 mmHg	I: 7% II: 0% III: 43%	III: >2000 mg/day in late pregnancy in 3	increased sCr in 2 women (III), stable in others
Carr 2006 [73]	MAP<100 (I) MAP≥100 (II)	Decrease in MAP in group II	I: 27.3% II: 42.9%	I: 33.3% nephrotic II: 72.2%	No difference in sCr and CCr between groups
How 2004 [72]	Prot<190 (I) 190-499 (II) >499 (III)	NR	I: 17% II: 20% III: 32.3%	NR	NR
Irfan 2004 [71]	-	72.7% exacerbation	27.3%	73% nephrotic 82% worsening	NR[a]
Bagg 2003 [70]	-	NR	NR	NR	NR[b]
Rossing 2002 [69]	Non-preg (I) Preg (II)	I: 139/85 mmHg II: 136/83 mmHg	NR	I: UAE 882 mg/day II: UAE 786 mg/day	I: 33% doubling baseline sCr, 24% ESRD II: 31% doubling baseline sCr, 23% ESRD
Khouri 2002 [68]	sCr≤1 (I) 1-1.5 (II) >1.5 (III)	NR	I: 41% II: 33.3% III: 44.4%	increase in all groups	CCr 9→34 weeks (ml/min): I: 87.8±22.1→ 92.7±28.6 II: 79.2±10.5→ 50.0±15.2 III: 41.5±6.2→ 45.4±2.1
Ekbom 2001 [67]	Normoalb (I) Microalb (II) Nephro (III)	without PtU: I: 5% II: 4% III: 0%	I: 6% II: 42% III: 64%	I: 0.5% nephrotic II: 23% III: 55%	NR
Sobczak 2000 [66]	Nephro (I) No nephro (II)	28.6%		Significant increase (3190±3790→7370±6100 mg/day)	sCr increase (mg/dl): 1.4±1.01→1.9±1.45
Biesenbach 2000 [65]	Nephro (I) No nephro (II)	NR	I: 60% II: 6%	I: 70% nephrotic II: 0%	NR
Schröder 2000 [64]	UAE>30 (I) BP ≥140/90 (II) Other (III)	6.9%	NR	15.7% UAE >30 mg/day; 12.7% UAE 30-300	NR

Legend: Medium-long term outcomes: [a] Irfan 2004: 63.6% need dialysis/transplantation (26 months from parturition). [b] Bagg 2003: 36% begun dialysis (follow-up 6 years). *Abbreviations*: ATG – above target group, BP – blood pressure, BTG – below target group, CCr – creatinine clearance, ctrl – control, DBP – diastolic blood pressure, ESRD – end-stage renal disease, GFR – glomerular filtration rate, DN – diabetic nephropathy, LN – lupus nephritis, MAP – mitogen-activated protein, microalb – microalbimuria, nephro – nephropathy, normoalb – normoalbimuria, NR – not reported, OR – odds ratio, PE – preeclampsia, PN – pyelonephritis, preg – pregnant, prot – proteinuria, PtU – proteinuria, sCr – serum creatinine, SBP – systolic blood pressure, trim – trimester, UAE – urinary albumin excretion, UTI – urinary tract infection, wk – week. [*]with severe microangiopathy. References [64-79].

Table 8. Main maternal outcomes from 1990-1999

Reference	Subgroups	Hypertension (pregnancy-induced)	Pre-eclampsia	Proteinuria	Kidney function in pregnancy
Biesenbach 1999 [63]	Normal CCr increase (I) Abnormal (II)	3rd trimester: I: 150 ± 16; 91 ± 7 mmHg II: 175 ± 18; 98 ± 7 mmHg	57.1%	64.2% nephrotic[c]	I: 0% worsening II: 87%
Dunne 1999 [62]	Mild (I) Moderate (II) Severe (III)	11% baseline 83% delivery	NR	19% high grade baseline; 47% delivery	NR[d]
Bar 1999 [61]	-	NR	46%	3rd trim: 33% grade 1, 63% grade 2, 4% grade 3	CCr stable throughout pregnancy[e]
Bar 1999 [60]	Primary renal disease (I) Nephropathy (II) Allograft (III)	NR	I: 22% II: 46% III: 17%	3rd trim: I: 42% (grade 0), 21% (1), 29% (2), 8% (3) II: 0% (grade 0), 33% (1), 63% (2), 4% (3) III: 44% (grade 0), 26% (1), 30% (2), 0% (3)	3rd trimester sCr (mg/dl): I: 0.99±0.82 II: 0.94±0.13 (p = 0.02) III: 1.40±0.70
Czajkowski 1999 [59]	White R (I) F (II) FR (III) T (IV)	I: 8/14 II: 2/3 III: 8/19 IV: 1/2	I: 4/14 II: 1/3 III: 11/19 IV: 1/2	50% (50% >3000 mg/day)	NR
Reece 1998	-	77% chronic	53%	100% >300 mg/day 1st trim	NR
Purdy 1996 [57]	Pregnant (I) Non-preg (II)	72.7% exacerbation	27.3%	73% nephrotic 82% worsening	Mean sCr (prepregnancy-3rd trimester): 1.8→2.5 mg/dl Renal function stable: 27%; transient worsening: 27%; permanent: 45%
Mackie 1996 [56]	Moderate (I) Early (II)	NR	NR	NR	different individual patterns, occasional worsening
Miodovnik 1996 [55]	Nephropathy (I) ESRD (Ia) Non-ESRD (Ib) No nephro (II) Nephro dev (IIa) No nephro (IIb)	I: 65% II: 19%	I: 65% II: 9%	I: >1500 mg/day in 75% II: NR	nephropathy developed in 13/136; ESRD in 12/46 with nephropathy
Gordon 1996 [54]	-	NR	53% (severe in 15.5%)	3rd trim.: 4820±4700 mg/day; follow-up: 2940±4260 mg/day	3rd trimester CCr: 105.3±47.1 ml/min
Hopp1995 [53]	White RF (I) CD (II)	NR	71% *	severe in 80%*	NR
Hod 1995 [52]	-	3rd trimester: 125±15; 81±11 mmHg Postpartum: 123±7; 80 ± 4 mmHg	37.5%	3rd trimester:1000±1185 mg/day; postpartum: 619±411 mg/day	3rd trimester sCr: 0.8±0.06 mg/dl; postpartum sCr: 0.9±0.07 mg/dl; 3rd trimester CCr: 117±21.8 ml/min; postpartum CCr: 107±21.8 ml/min
Kimmerle 1994 [51]	Nephropathy (I) No nephro (II)	3rd trimester: I: 152±16; 90±10 mmHg II: NR	I: 19% II: NR	I: 5000 mg/day 3rd trim.; 53% >3000 mg/day II: NR	I: sCr increased >15% in pregnancy in 39% II: NR
Combs 1993 [50]	Prot<190 (I) 190-499 (II) >500 (III)	I: 20% II: 47% III: 52%	I: 10% II: 40% III: 47%	NR	NR
Biesenbach 1992 [49]	-	3rd trimester 173±14; 99±5 mmHg	60% eclampsia	3rd trimester: 8600±5000 mg/day (2.8-fold increase)[f]	3rd trimester sCr: 2.0±0.5 mg/dl (increase of 54%); 3rd trimester CCr: 48 ± 26 ml/min (decline of 25%)

Legend: Medium-long term outcomes: [c] Biesenbach 1999: protein excretion to pre-conceptional values 3-6 months after delivery; [d] Dunne 1999: one patient reached ESRD and received hemodialysis; [e] Bar 1999: no deterioration in renal function in any patient after two years; [f] Biesenbach 1992: proteinuria returned to pre-pregnancy within 3-6 months. *Abbreviations*: ATG – above target group, BP – blood pressure, BTG – below target group, CCr – creatinine clearance, ctrl – control, DBP – diastolic blood pressure, ESRD – end-stage renal disease, GFR – glomerular filtration rate, DN – diabetic nephropathy, LN – lupus nephritis, MAP – mitogen-activated protein, microalb – microalbimuria, nephro – nephropathy, normoalb – normoalbimuria, NR – not reported, OR – odds ratio, PE – preeclampsia, PN – pyelonephritis, preg – pregnant, prot – proteinuria, PtU – proteinuria, sCr – serum creatinine, SBP – systolic blood pressure, trim – trimester, UAE – urinary albumin excretion, UTI – urinary tract infection, wk – week. *with severe microangiopathy. References [49-63].

Table 9. Main maternal outcomes from 1980-1989

Reference	Subgroups	Hypertension (pregnancy-induced)	Pre-eclampsia	Proteinuria	Kidney function in pregnancy
Biesenbach 1989 [48]	Microalb (I) Normoalb (II)	No significant difference between the groups	NR	I: 10.0-fold increase in protein excretion II: 5.7-fold increase	No significant difference between the groups
Reece 1988 [12]	-	61% BP increased	35%	71% nephrotic[g]	35% increased sCr, 52% stable or decreased
Biesenbach 1987 [47]	Normoalb (I) Microalb (II) Prot (III)	Worsened	NR	3-8 fold increase	CCr decline in cases with pre-existing overt proteinuria
Kitzmiller 1981 [46]	-	37%; worsened in 37.5%	3.8%	58% >6000 mg/day[h]	CCr without increase in pregnancy: 3rd trimester sCr: 42% <1 mg/dl, 46% 1.1-1.9 mg/dl, 12% >2 mg/dl

Legend: Medium-long term outcomes: [g] Reece 1988: proteinuria increases reverted in puerperium. [h] Kitzmiller 1981: proteinuria declined >50% in 65.2% 6-35 months after pregnancy White class B: onset at age 20 or older or duration < 10 years; class C: onset at age 10-19 or duration 10-19 years; class D: onset < 10 or duration > 20 years; class E: overt diabetes mellitus with calcified pelvic vessels; class F: diabetic nephropathy; class R: proliferative retinopathy; class RF: retinopathy and nephropathy; class H: ischemic heart disease; class T: prior kidney transplant. *Abbreviations*: ATG – above target group, BP – blood pressure, BTG – below target group, CCr – creatinine clearance, ctrl – control, DBP – diastolic blood pressure, ESRD – end-stage renal disease, GFR – glomerular filtration rate, DN – diabetic nephropathy, LN – lupus nephritis, MAP – mitogen-activated protein, microalb – microalbimuria, nephro – nephropathy, normoalb – normoalbimuria, NR – not reported, OR – odds ratio, PE – preeclampsia, PN – pyelonephritis, preg – pregnant, prot – proteinuria, PtU – proteinuria, sCr – serum creatinine, SBP – systolic blood pressure, trim – trimester, UAE – urinary albumin excretion, UTI – urinary tract infection, wk – week. References [12, 46-48].

Table 10. Main fetal outcomes from 2000-2012

Reference	Subgroups	Birth weight (g)	SGA/IUGR	Cesarean delivery	Preterm delivery	Stillbirth/neonatal death
Bell R 2012 [79]	Type I (I) Type II (II)	Major congenital anomaly in women with diabetes: RR 3.8 Multivariate analysis: peri-conception HbA1c and pre-pregnancy nephropathy were significant independent predictors of congenital anomaly; pre-pregnancy nephropathy OR 2.5				
Themeli Y 2012 [78]	Ctrl (I) Microalb (II) Nephro (III)	I: 3.478±595 II: 3.124±678 III: 2.185±1.042	I: 1.8% SGA II: 5.5% III: 37.5%	NR	I: 3.6% <37, 0% <34 weeks II: 11.1% <37, 5.5% <34 weeks III: 50% <, 25% <34 weeks	I: 0% perinatal mortality II: 5.5% III: 0%
Young EC 2011 [77]	No nephro (I) Nephro (II)	I: 3290 II: 2710	I: 12.5% SGA II: 40%	NR	I: 12.5% II: 63.6%	NR
Yogev Y 2010 [76]	No compl (I) Compl (II)	I: 3223±318 II: 3187±1143	I: 0% SGA II: 7%	I: 67% II: 78%	I: 0% II: 32%	I: 0% stillbirths II: 6%
Jensen DM 2010 [75]	Ctrl (I) Microalb (II)	I: 3650 (3162-4060) II: 3335 (2900-3650)	NR	NR	I: 37% <37, 6% <34 weeks II: 36% <37, 13% <34 weeks	I: 3% perinatal mortality II: 5%
Nielsen LR 2009 [74]	Normoalb (I) Microalb (II) Nephro (III)	I: 3540 (445-5620) II: 3430 (2510-4484) III: 2765 (2040-3730)	I: 1% SGA II: 0% III: 29%	NR	I: 20% <37, 1% <34 weeks II: 20% <37, 0% <34 weeks III:71% <37, 14%<34 weeks	I: 2% perinatal mortality II: 0% III: 0%
Carr DB 2006 [73]	MAP<100 (I) MAP≥100 (II)	I: 2520 ±150 II: 1880 ±200	I: 9.1% SGA II: 28.6%	I: 63.4% II: 76.2%	I: 4.6% <32 weeks II: 38.1%	I: 9.1% fetal demise II: 9.5%
How HY 2004 [72]	Prot<190 (I) 190-499 (II) >499 (III)	I: 3170±880 II: 3022 ±1051 III: 2447±903	NR	NR	I: 13% <34 weeks II: 14% III: 29%	NR
Irfan S 2004 [71]	-	NR	NR	NR	NR	NR
Bagg W 2003 [70]	-	2950 (730-3780)	NR	83.3%	46% <35 weeks	NR
Rossing K 2002 [69]	Non-preg (I) Preg (II)	II: 2535	NR	II: 38.7%	NR	II: 12.9% neonatal death
Khouri JC 2002 [68]	sCr≤1 (I) 1-1.5 (II) >1.5 (III)	NR	I: 7.7% SGA II: 8.3% III: 33.3%	I: 76.9% II: 91.7% III: 88.9%	I: 7.7% <32 weeks II: 16.7% III: 44.4%	I: 5.1%; perinatal mortality II: 0% III: 11.1%
Ekbom P 2001 [67]	Normoalb (I) Microalb (II) Nephro (III)	I: 3553±672 II: 3124±767 III: 2235±1038	I: 2% SGA II: 4% III: 45%	NR	I: 35% <37, 6% <34 weeks II: 62% <37, 23% <34 weeks III: 91% <37, 45% <34 weeks	I: 1.5% perinatal mortality: II: 4%; III: 0%
Sobczak M 2000 [66]	Nephro (I) No nephro (II)	I: 2105 II: 3271	I: 26.3% IUGR II: 5.9%	NR	I: 66.6% <37, 57.1% <34 weeks II: 26.1% <37, 7.5% < 34 weeks	I: 15.9% perinatal mortality II: 3.2%
Biesenbach G 2000 [65]	Nephro (I) No nephro (II)	I: 2250±496 II: 3544±435	I: 50% SGA II: 0%	I: 60% II: 60%	I: 60% <34 weeks II: 0%	NR
Schroder W 2000 [64]	UAE>30 (I) BP ≥140/90 (II) Other (III)	NR	NR	NR	NR	NR

Legend: White class B: onset at age 20 or older or duration < 10 years; class C: onset at age 10-19 or duration 10-19 years; class D: onset < 10 or duration > 20 years; class E: overt diabetes mellitus with calcified pelvic vessels; class F: diabetic nephropathy; class R: proliferative retinopathy; class RF: retinopathy and nephropathy; class H: ischemic heart disease; class T: prior kidney transplant. *Abbreviations*: BP – blood pressure, Compl – complications, Ctrl – control, IUGR – intrauterine growth restriction, LN – lupus nephritis, Macroalb – macroalbuminuria, MAP – mitogen-activated protein, Microalb – microalbuminuria, MPGN – membranoproliferative glomerulonephritis, Nephro - nephropathy, Normoalb – normoalbuminuria, NR – not reported, OR – odds ratio, Preg – pregnant, Prot – proteinuria, RR – relative risk, sCr – serum creatinine, SGA – small for gestational age, SLE – systemic lupus erythematosis, UAE - urinary albumin excretion. References [64-79].

Table 11. Main fetal outcomes from 1990-1999

Reference	Subgroups	Birth weight (g)	SGA/IUGR	Cesarean delivery	Preterm delivery	Stillbirth/neonatal death
Biesenbach G 1999 [63]	Norm CCr incr (I) Abnormal (II)	1893±712	64.2% SGA	50%	64.2% <34 weeks	14.2% stillbirths
Dunne FP 1999 [62]	Mild (I) Moderate (II) Severe (III)	2429 (985-4140)	14% SGA	90.5%	57.2% <37 weeks	2 neonatal death
Bar J 1999 [61]	-	NR	21% IUGR	62.5%	17% <37 weeks	4.2% stillbirths
Bar J 1999 [60]	Prim renal dis (I) Nephro (II) Allograft (III)	NR	I: 13% IUGR II: 21% III: 33%	I: 24% II: 62.5% III: 36%	I: 22% <37 weeks II: 17% III: 62%	I: 0% stillbirths II: 4.2% III: 7%
Czajkowski K 1999 [59]	White R (I) F (II) FR (III) T (IV)	NR	NR	NR	NR	Apgar ≤7: 7/44
Reece EA 1998 [58]	-	2687 (940-4280)	9% IUGR	63%	26% <36 weeks	5% neonatal death
Purdy LP 1996 [57]	Preg (I) Non-preg (II)	2125 (540-3575)	7.1% IUGR	36%	78.6% <37 weeks	None
Mackie ADR 1996 [56]	Moderate (I) Early (II)	I: 1970 (670-2960) II: 2600 (1800-4060)	I: 16.67% SGA II: 9%	I: 100% II: 100%	I + II: 26% <20 weeks	NR
Miodovnik M 1996 [55]	Nephro (I) ESRD (Ia) No ESRD (Ib) No nephro (II) Nephro (IIa) No nephro (IIb)	I: 2745±809 II: 3401±710	I: 9% IUGR II: 4%	I: 76% II: 69%	I: 57% <37, 22% <34 weeks II: 25% <37, 10% <34 weeks	I: 9% still-births/neonatal death II: 1%
Gordon M 1996 [54]	-	2623±818	11% IUGR	80%	15.5% <34 weeks; 35.5% 34-36 weeks	None
Hopp H 1995 [53]	White RF (I) CD (II)	I: 2981 II: NR	I: 7/76 II: 2/85	I:70/76 II: 42/85	I+II: 39%	I+II: 5% perinatal mortality
Hod M 1995 [52]	-	2140-3870	12.5% SGA	75%	12.5% <37 weeks	None
Kimmerle R 1994 [51]	Nephro (I) No nephro (II)	Ia: 2670±776 Ib: 1640±607 II: 3565±748	Ia: 19% SGA Ib: 30% II: 1.8%	Ia: 80% Ib: 100% II: 64%	Ia: 19% <34 weeks Ib: 60% II: 2.7%	None
Combs CA 1993 [50]	Prot<190 (I) 190-499 (II) >500 (III)	I: 3445±725 II: 3063±991 III: 2788±790	NR	NR	I: 23% <37, 8% <34 weeks II: 51% <37, 11% <34 weeks III: 60% <37, 23% <34 weeks	NR
Biesenbach G 1992 [49]	-	1312	20% SGA	60%	100% <36 weeks	60% perinatal mortality

Legend: White class B: onset at age 20 or older or duration < 10 years; class C: onset at age 10-19 or duration 10-19 years; class D: onset < 10 or duration > 20 years; class E: overt diabetes mellitus with calcified pelvic vessels; class F: diabetic nephropathy; class R: proliferative retinopathy; class RF: retinopathy and nephropathy; class H: ischemic heart disease; class T: prior kidney transplant. *Abbreviations*: BP – blood pressure, Compl – complications, Ctrl – control, ESRD – end-stage renal disease, IUGR – intrauterine growth restriction, LN – lupus nephritis, Macroalb – macroalbuminuria, MAP – mitogen-activated protein, Microalb – microalbuminuria, MPGN – membranoproliferative glomerulonephritis, Nephro - nephropathy, Normoalb – normoalbuminuria, NR – not reported, OR – odds ratio, Preg – pregnant, Prot – proteinuria, RR – relative risk, sCr – serum creatinine, SGA – small for gestational age, SLE – systemic lupus erythematosis, UAE - urinary albumin excretion. References [49-63].

Table 12. Main fetal outcomes from 1980-1989

Reference	Subgroups	Birth weight (g)	SGA/IUGR	Cesarean delivery	Preterm delivery	Stillbirth/neonatal death
Biesenbach G 1989 [48]	Microalb (I) Normoalb (II)	NR	NR	NR	NR	NR
Reece EA 1988 [12]	-	2808.6±807	16% SGA	70%	54%	6% death in utero 6.5% stillbirth
Biesenbach G 1987 [47]	Normoalb (I) Microalb (II) Prot (III)	NR	NR	NR	NR	NR
Kitzmiller JL 1981 [46]	-	2295	20.8% IUGR	76.9%	30.8%	7.7% fetal death 4% neonatal death

Legend: White class B: onset at age 20 or older or duration < 10 years; class C: onset at age 10-19 or duration 10-19 years; class D: onset < 10 or duration > 20 years; class E: overt diabetes mellitus with calcified pelvic vessels; class F: diabetic nephropathy; class R: proliferative retinopathy; class RF: retinopathy and nephropathy; class H: ischemic heart disease; class T: prior kidney transplant. *Abbreviations*: IUGR – intrauterine growth restriction, Microalb – microalbuminuria, Normoalb – normoalbuminuria, NR – not reported, Prot – proteinuria, RR – relative risk, SGA – small for gestational age. References [49-63].

Table 13. Main fetal outcomes in patients with type 1 diabetes, microalbuminuria, and nephropathy homogeneously defined in Themeli 2012, Nielsen 2009, and Ekbom 2001

Cases (n)	SGA cases (%)	Preterm delivery, < 37 weeks cases (%)	Preterm delivery, < 34 weeks cases (%)	Perinatal death or stillbirths, cases (%)
Normoalbuminuria: 357	6 (1.68%)	93 (26.05%)	13 (3.64%)	5 (1.40%)
Microalbuminuria: 54	2 (3.70%)	20 (37.04%)	7 (12.92%)	2 (3.70%)
Nephropathy: 26	10 (38.46%)	19 (73.08%)	8 (30.77%)	0
Stat. significance:	p = 0.31	p = 0.09	p = 0.003	p = 0.22
Normo vs. micro	p < 0.0001	p < 0.0001	p < 0.0001	p = 0.39
Normo vs. nephro	p < 0.0001	p = 0.0025	p = 0.055	p = 0.20
Micro vs. nephro				

Legend: Normo – normoalbuminuria, Micro – microalbuminuria, Nephro – diabetic nephropathy, SGA – small for gestational age.

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