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Preeclampsia and Diabetes

Tracey L. Weissgerber[1] and **Lanay M. Mudd**[2]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN

[2]Department of Kinesiology, Michigan State University, East Lansing, MI

Abstract

Preeclampsia is diagnosed in women presenting with new onset hypertension accompanied by proteinuria or other signs of severe organ dysfunction in the second half of pregnancy. Preeclampsia risk is increased two to four-fold among women with type 1 or type 2 diabetes. The limited number of pregnant women with preexisting diabetes and difficulties associated with diagnosing preeclampsia in women with proteinuria prior to pregnancy are significant barriers to research in this high-risk population. GDM also increases preeclampsia risk, although it is unclear whether these two conditions share a common pathophysiological pathway. Non-diabetic women who have had preeclampsia are more likely to develop type 2 diabetes later in life. Among women with type 1 diabetes, a history of preeclampsia is associated with an increased risk of retinopathy and nephropathy. More research examining pathophysiology, treatment and the long-term health implications of preeclampsia among women with preexisting and gestational diabetes is needed.

Keywords

preeclampsia; type 1 diabetes; type 2 diabetes; gestational diabetes

Introduction

Preeclampsia is a leading cause of maternal [1] and fetal [2] morbidity and mortality. In developed countries, this syndrome affects 2-7% of pregnancies in non-diabetic women [3, 4]. Type 1 diabetes, type 2 diabetes and gestational diabetes further increase preeclampsia risk. Preeclampsia is diagnosed in women presenting with new onset hypertension and proteinuria during the second half of pregnancy [5]. New guidelines from the American College of Obstetrics and Gynecology (ACOG) indicate that preeclampsia can also be diagnosed in the absence of proteinuria in hypertensive women with pulmonary edema, progressive renal insufficiency, impaired liver function, thrombocytopenia, or new onset cerebral or visual disturbances [5]. Delivery is the only known cure for preeclampsia, and effective prevention strategies are lacking. Preeclampsia also has long-term health implications. The American Heart Association recently recognized preeclampsia as a risk factor for future cardiovascular disease [6] and stroke [7] in women.

Address for Correspondence: Tracey L. Weissgerber, Ph.D. Division of Nephrology & Hypertension, Mayo Clinic, 200 1st St. SW, RO-HA-06-675B-5, Rochester, MN 55905, Phone: (507) 266-2844, weissgerber.tracey@mayo.edu.

The pathophysiology of preeclampsia remains elusive. Current theories suggest that the clinical features of this syndrome are caused by systemic maternal endothelial dysfunction resulting from a combination of preexisting maternal risk factors and abnormal placental development [8]. Maternal risk factors include pre-pregnancy obesity, advanced maternal age, black race, and chronic hypertension and other cardiovascular risk factors [8]. These maternal characteristics may contribute to oxidative stress, inflammation and vascular dysfunction, all of which have been implicated in the etiology of preeclampsia [8]. At the placental level, failed adaptation of the uterine spiral arteries may cause hypoxia [8], repeated ischemia-reperfusion injury [9], or high velocity blood flow in the intervillous space [10]. The damaged placenta is believed to release one or more factors into the maternal circulation that contribute to vascular dysfunction [8]. Possible candidates for this placental factor include the anti-angiogenic proteins soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) [11, 12]. sFlt-1 lowers the bioavailability of vascular endothelial growth factor (VEGF) and placental growth factor (PGF) by binding these pro-angiogenic ligands as a non-signaling decoy [13]. sEng inhibits binding of transforming growth factor β1 to endoglin, preventing endothelial nitric oxide synthase activation and subsequent vasodilation [12]. Thus, excessive sFlt-1 and sEng may impair pregnancy-induced adaptation in maternal placental bed vessels and contribute to systemic maternal endothelial dysfunction in some women with preeclampsia [13].

Insulin resistance has also been hypothesized to contribute to the pathophysiology of preeclampsia. Compared to women who have normotensive pregnancies, women who develop preeclampsia are more insulin resistant prior to pregnancy [14], in the first and second trimesters [15], and years after pregnancy [16]. This effect is partially explained by the fact that many preeclampsia risk factors are also associated with insulin resistance, including obesity, advanced maternal age, non-white race, chronic hypertension, diabetes and gestational diabetes [15, 14]. However, insulin resistance at 22-26 weeks gestation was a significant independent predictor of preeclampsia after adjustment for these common risk factors, suggesting an independent effect [15].

This review examines the relationship between preeclampsia and diabetes, focusing on new research in three key areas. The first section describes the unique challenges of studying preeclampsia in women with diabetes, and reviews recent studies examining preeclampsia pathophysiology in women with type 1 or type 2 diabetes. The second section examines the relationship between gestational diabetes and preeclampsia, along with the possibility of a shared pathophysiological pathway for these two conditions. The third section focuses on long-term risk of diabetes and diabetic complications in women with a history of preeclampsia.

Preeclampsia in Women with Type 1 or Type 2 Diabetes

Preexisting diabetes is a risk factor for preeclampsia. In comparison to the relatively low incidence of preeclampsia in non-diabetic women (2-7%) [3, 4], preeclampsia is diagnosed in15-20% of pregnancies in women with type 1 diabetes [17-19] and 10-14% of pregnancies in women with type 2 diabetes [20, 19]. Obesity is a shared risk factor for both preeclampsia and type 2 diabetes, however the greater preeclampsia risk among women with type 2

diabetes persists even when women are matched for BMI [21]. In a population-based study of deliveries in Washington state, preexisting diabetes was a risk factor for both early onset (diagnosis before 34 weeks gestation; hazard ratio (HR): 1.87, 95% confidence interval (CI): 1.60-2. 81) and late onset (HR: 2.46, 95% CI: 2.32-2.61) preeclampsia [22]. Known risk factors for preeclampsia among women with type 1 and type 2 diabetes include nulliparity, advanced maternal age, previous preeclampsia, hypertension, a longer duration of diabetes, microalbuminuria, nephropathy and retinopathy and poor glycemic control [23-25].

Preeclampsia research in women with type 1 and type 2 diabetes is complicated by two factors. First, multicenter studies and recruitment for an extended time period are often required to obtain a sufficient number of preeclamptic women with diabetes. Many investigators address this challenge by pooling women with type 1 and type 2 diabetes, or by combining women with diabetes with other high-risk groups (i.e. chronic hypertension, multi-fetal gestation, preeclampsia in a previous pregnancy, etc.). Recent guidelines for the standardization of preeclampsia study design strongly discourage this approach, as preeclampsia pathophysiology may differ among high-risk groups [26].

The second problem is the lack of standardized criteria for preeclampsia diagnosis in women who have proteinuria prior to conception, which is common in women with diabetes. The diagnosis of preeclampsia is straightforward in a subset of patients who develop the most severe forms of preeclampsia, such as the convulsive form, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets. For other patients, a variety of modified criteria are used. These include worsening proteinuria and/or other signs of organ dysfunction, such as a serum aminotransferase concentration of ≥70 U per liter, thrombocytopenia, or hypertension with severe headaches or epigastric pain [27, 28]. These diverse criteria make comparisons between studies difficult. In addition, worsening proteinuria during pregnancy is common in women with diabetic nephropathy [29] due to increases in the glomerular filtration rate [30]. Studies are needed to determine whether the recently expanded ACOG criteria for diagnosing preeclampsia in pregnant women who do not have proteinuria [5] also have diagnostic utility among women with preexisting proteinuria.

Despite these challenges, recent studies examining the pathophysiology of preeclampsia in women with type 1 diabetes have focused on the potential roles of angiogenic imbalance and haptoglobin phenotype.

Angiogenic Imbalance

Anti-angiogenic factors and preeclampsia risk have been extensively examined. However, many studies have excluded women with diabetes, or combined women from different high-risk populations. Studies examining the relationship between anti-angiogenic (sFlt-1, sEng) and pro-angiogenic (PGF) factors and preeclampsia in women with preexisting diabetes have yielded conflicting results. The largest study examined plasma angiogenic factors at 26 weeks gestation among 540 women with type 1 diabetes [31]. Compared to women who did not develop preeclampsia, women who later developed preeclampsia (n=94) had higher plasma sFlt-1 and sEng, and lower PGF [31]. The addition of sFlt-1:PGF slightly improved the performance of predictive models based on traditional preeclampsia risk factors [31].

Smaller longitudinal studies have examined these markers in women with type 1 diabetes who did not have microalbuminuria in early pregnancy [32], women with preexisting diabetes that required insulin [33], and a mixed group of women with type 1 or type 2 diabetes [34]. sFlt-1, sEng and PGF prior to 25 weeks gestation did not differ between diabetic women who developed preeclampsia and those who did not [34, 32, 33]. After 25 weeks gestation, results were conflicting. Whereas some studies reported lower PGF [34, 32], higher sFlt-1 [32] or higher sEng [33] among women who developed preeclampsia, others found no differences in PGF [33], sFlt-1 [34, 33] or sEng [32]. In addition to the small sample sizes and varying inclusion criteria, differences in sample type and processing may also contribute to the heterogeneity of results. Angiogenic markers were measured in plasma [31], serum [33, 32] or both [34], and few details regarding sample processing were provided. Angiogenic factors released from platelets and other blood components during sample processing can dramatically increase measured concentrations [35]. The collection of samples with cell activation inhibitors has been shown to reduce maternal serum PGF by 29% and sFlt-1 by 20% [35]. Larger studies with appropriate sample processing techniques are needed. Additional studies of angiogenic factors in relation to preeclampsia risk among women with type 2 diabetes would be beneficial, as most studies focus on type 1 diabetes.

Haptoglobin

Haptoglobin (Hp) is an anti-oxidant [36] and pro-angiogenic [37] protein best known for its ability to bind free hemoglobin following hemolysis. Hp has three common, genetically-determined phenotypes (1-1, 2-1, 2-2) [38]. Hp 1-1 is the strongest antioxidant [36], whereas Hp 2-2 is the most angiogenic [37].

Several factors suggested that Hp phenotype could potentially be important in preeclampsia. First, oxidative stress and angiogenic imbalance are important pathophysiological processes in preeclampsia [11, 39]; therefore it is reasonable to think that Hp phenotype might influence preeclampsia risk. Second, cardiovascular event risk is doubled in Hp 2-2 individuals with diabetes, compared to Hp 1-1 and 2-1 individuals with diabetes [40-42]. Additionally, Hp phenotype influences responsiveness to antioxidant vitamins in individuals with diabetes. Daily vitamin E supplementation eliminates the increased cardiovascular disease risk seen in Hp 2-2 individuals with type 2 diabetes, but has no effect in Hp 2-1 or 1-1 individuals with diabetes [43, 42, 44]. In contrast, vitamin C combined with vitamin E may be beneficial or harmful depending on phenotype [41]. These findings are of particular interest to preeclampsia researchers. Oxidative stress is associated with preeclampsia [11, 39] and the antioxidant vitamins C and E lowered preeclampsia incidence by 60% among high-risk women in a small randomized controlled trial (RCT) [45]. Unfortunately, subsequent RCTs in high [46-50] and low [51] risk women, and women with type 1 diabetes [28] were negative. These disparate results are likely due to low power in the small trial. However, differences could also be explained by the greater diversity of patients in multicenter trials masking a subset of responsive women.

Small case-control studies of non-diabetic women have reported that preeclampsia risk was increased, [52], decreased [53, 54], or not different [55] in women with the stronger antioxidant Hp 1-1 phenotype. The heterogeneity of results may have been due to

differences in the populations studied. However, the small sample sizes and lack of consistent findings suggest that Type II error may have been a factor. To address these issues, Weissgerber *et al*. conducted secondary analyses of two larger RCTs of daily vitamin C and E supplementation to prevent preeclampsia. The first examined low risk primiparous women [51], while the second enrolled women with type 1 diabetes [28]. Hp phenotype was not associated with preeclampsia risk in either trial [56, 57]. Furthermore, the authors found no evidence that vitamins C and E prevented preeclampsia in women of any Hp phenotype [56, 57]. Despite proven effects in other disease states, it appears that Hp phenotype does not play a significant role in preeclampsia risk or responsiveness to antioxidant vitamin supplementation to prevent preeclampsia.

Preeclampsia and Gestational Diabetes

Gestational diabetes mellitus (GDM) is defined as hyperglycemia that is first diagnosed during pregnancy. The American Diabetes Association (ADA) recommends using either the traditional two-step approach or a newer one step approach to screen for GDM at 24-28 weeks gestation. For the two-step approach, women who fail a 50-g glucose challenge test complete a second diagnostic 75-g oral glucose tolerance test to confirm the diagnosis [58]. The newer one-step approach is based on a single 75-g oral glucose tolerance test and was developed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), which includes the ADA. GDM is diagnosed if fasting (≥92 mg/dl), one hour (≥180 mg/dl) or two hour (≥153 mg/dl) glucose values exceed established cut points [58].

The prevalence of GDM ranges from 2-10% of all pregnancies in developed countries [59]; however, those rates are expected to rise drastically with the adoption of the less restrictive IADPSG diagnostic criteria [60]. GDM is associated with birth complications, including macrosomia and operative delivery. Long-term health risks associated with GDM include an increased risk of type 2 diabetes for both the woman and her child [61-63].

GDM and preeclampsia share many risk factors, including advanced maternal age, nulliparity, multifetal pregnancies, non-white race/ethnicity and pre-pregnancy obesity [64, 65]. GDM is often listed as a risk factor for the development of preeclampsia; however, previous research on the co-occurrence of the two conditions has often been underpowered and/or failed to account for shared risk factors such as obesity. To address these issues, a retrospective investigation of 647,392 pregnancies in the German Perinatal Quality Registry examined the relation between GDM and preeclampsia while controlling for common risk factors. The authors found that the odds of preeclampsia were increased among women with GDM (adjusted odds ratio (aOR): 1.29, 95% CI: 1.19-1.41), even after controlling for age, nationality, job status, smoking, parity, multifetal pregnancy, pre-pregnancy weight status and gestational weight gain [65]. These results concur with other birth registry studies in Canada and Sweden, confirming that GDM is an independent risk factor for preeclampsia [66, 67].

One study sought to identify the most salient clinical risk factors for preeclampsia among women with GDM [68]. First trimester obesity (defined as BMI ≥ 27 kg/m^2; aOR: 10.4, 95% CI: 5.3-20.8), GDM diagnosis prior to 20 weeks gestation (aOR: 8.0, 95% CI: 4.3-14.9)

and poor glycemic control (aOR: 8.4, 95% CI: 5.6-15.4) were the most significant risk factors for preeclampsia [68]. Among these, maternal obesity may be the most modifiable risk factor, although new results also identify excessive gestational weight gain as an independent modifiable risk factor for preeclampsia. A study of 2037 women with GDM assessed the effects of pre-pregnancy weight status, gestational weight gain and third trimester glycemic control (via glycatedhemoglobin or HbA_{1c}) on the risk of pregnancy-induced hypertension (including preeclampsia and new-onset hypertension after 20 weeks gestation) [69]. The authors found that poor glycemic control (aOR: 2.5, 95% CI 1.1-5.7) and pre-pregnancy obesity (aOR: 8.9, 95% CI: 5.0-16.0) were associated with increased risk of pregnancy-induced hypertension, but excessive gestational weight gain also increased risk (aOR: 1.9, 95% CI: 1.1-3.4) [69]. The prevalence of pregnancy-induced hypertension was highest among obese women who gained excessive weight (41%). In another study specific to preeclampsia, excessive gestational weight gain was associated with non-significantly increased odds of preeclampsia (aOR: 1.4; 95% CI: 0.6-3.1) compared to appropriate weight gain; however, when weight gain was expressed continuously, every one lb/wk increase in weight gain after GDM diagnosis was associated with a 1.8-fold increased odds of preeclampsia [70]. Taken together, these results indicate that while excess gestational weight gain may increase preeclampsia risk among women with GDM, preexisting obesity confers a greater risk.

It is unclear whether a common etiologic pathway underlies both GDM and preeclampsia. When compared to women with healthy pregnancies, researchers have identified many maladaptations to pregnancy that are present in both preeclampsia and GDM. These include endothelial dysfunction (e.g., lower flow-mediated dilation) [71, 72], angiogenenic imbalance (e.g., high sFlt-1 and/or low PGF) [71, 73], increased oxidative stress (e.g., low total antioxidant status, high free radicals) [74], and dyslipidemia (e.g., increased triglycerides) [75, 76]. However, it is difficult to know whether abnormalities in these biomarkers result from a common etiology, or are responses to different underlying disease processes in women with preeclampsia and GDM. For example, Wen *et al*. [77] postulate that pre-pregnancy susceptibility to cardiovascular disease sets the stage for preeclampsia. Poor placentation leads to systemic endothelial dysfunction and inflammation, which is reflected by the biomarkers stated above. In contrast, they argue that GDM has pre-pregnancy origins in beta cell dysfunction that is only unmasked by the progressive insulin resistance of pregnancy [77]. The resulting hyperglycemia causes endothelial damage and inflammation, as captured by the above biomarkers [77]. In fact, others have postulated that insulin resistance during pregnancy could be the common trigger leading to GDM and/or preeclampsia in predisposed women [78]. At present, none of these theories have been adequately tested.

One way to assess whether GDM and preeclampsia share a common etiology would be to determine whether interventions to treat GDM also reduce preeclampsia risk. A randomized control trial of treatment (nutritional counseling, diet therapy, and insulin if needed) vs. no treatment among almost 1000 women with mild GDM found that treatment was associated with 55% reduced risk of preeclampsia (RR: 0.46; 95% CI: 0.22-0.97) [79]. However, other trials have failed to find significant effects [80, 81]. A recent meta-analysis of 10 GDM

treatment trials (of which only 3 examined preeclampsia rates), found no association between GDM treatment and preeclampsia (RR=1.14, 95% CI: 0.24-5.45) [82]. The wide confidence intervals of the studies included in the meta-analysis demonstrate that additional adequately powered studies are needed to determine whether GDM treatment lowers preeclampsia risk.

The Risk of Diabetes After a Preeclamptic Pregnancy

While preeclampsia is now recognized as a risk factor for cardiovascular disease [6] and stroke [7], the relationship between preeclampsia and future diabetes has received less attention. A classic study by Chesley reported an increased risk of late onset diabetes among women with a history of eclampsia [83]. This severe form of preeclampsia causes seizures and leads to very high rates of maternal and fetal morbidity and mortality. Recent studies suggest that preeclampsia is also a risk factor for future diabetes (Table 1) [84-88]. This effect is evident even when women who had preeclampsia with gestational diabetes are excluded [84, 85]. However, preeclampsia is a modest predictor of future diabetes when compared to gestational diabetes (Table 1). When considering both pregnancy conditions, the risk of developing diabetes is moderately increased in women who had preeclampsia (without gestational diabetes), greatly elevated in women who had gestational diabetes (without preeclampsia), and highest in women who had both preeclampsia and gestational diabetes [84, 85]. A registry study of 226,832 women in Norway showed that only 0.5% of women without GDM or preeclampsia had received a prescription to treat diabetes within five years of birth, while 2% of women with preeclampsia had received such a prescription, 19% of women with GDM diagnoses were taking diabetes drugs and over half (55%) of women with both conditions had received a diabetes prescription [84]. Feig and colleagues similarly reported that the number of women that would need to be followed for five years to detect one case of diabetes was 123 for preeclampsia, 68 for gestational diabetes, and 31 for preeclampsia and gestational diabetes [85].

Existing studies of long-term diabetes risk either did not distinguish between type 1 and type 2 diabetes [84, 85, 87], or focused on type 2 diabetes [86]. Authors of the studies that pooled type 1 and 2 diabetes speculated that the increased risk that they observed was likely due to type 2 diabetes, as type 1 diabetes is usually diagnosed in childhood or adolescence. Only one study examined the risk of type 1 and type 2 diabetes separately [88]. Women who had preeclampsia were significantly more likely to be hospitalized for type 2 diabetes (aOR: 2.0, 95% CI: 1.3-3.2), but not type 1 diabetes (aOR: 1.8, 95% CI: 0.8-3.8), within one year of delivery [88]. Low power may have contributed to the absence of a significant effect for type 1 diabetes. The adjusted odds ratios for type 1 and type 2 diabetes were very similar (1.8 vs. 2.0), but fewer women were hospitalized for type 1 diabetes (n = 71 vs. 212 [88]). Regardless, the fact that 25% of the women hospitalized for diagnosis of diabetes within one year of delivery had type 1 diabetes [88] questions the previous authors' assumption that estimated effects of preeclampsia on a pooled “diabetes” variable predominantly reflects type 2 diabetes risk.

Additional studies of type 1 diabetes risk following a preeclamptic pregnancy are clearly warranted, and they should address three important limitations of the only study on type 1

diabetes to date [88]. First, the primary outcome of hospitalization for diabetes likely contributed to the high proportion of women with type 1 diabetes. Compared to type 2 diabetes, the more severe clinical features of type 1 diabetes may lead to higher hospitalization rates. Second, women were followed for one year after delivery. While some non-diabetic women may have developed diabetes during that time, others likely had preexisting diabetes that had never been diagnosed. Third, the study examined women who delivered in New York City [88]. Rates of diagnosis for type 1 diabetes may be very different in other cohorts, as they likely depend on maternal age, length of follow-up, access to health care and other factors.

Diabetic Complications in Women with Type 1 Diabetes After a Preeclamptic Pregnancy

Several studies suggest that women with preexisting type 1 diabetes who have had preeclampsia are more likely to develop diabetic complications later in life. Gordin and colleagues examined the risk of diabetic nephropathy, hypertension and coronary heart disease among 203 Finnish women with type 1 diabetes [89]. After an average follow-up of 11 years, women who had preeclampsia were more likely to be taking anti-hypertensive medication than women who had normotensive pregnancies (50% vs. 10%) [89]. They were also more likely to have coronary heart disease (12% vs. 2%), myocardial infarction (7% vs. 0%), and diabetic nephropathy (42% vs. 9%) [89]. Preeclampsia and HbA_{1c} during pregnancy were both independent predictors of diabetic nephropathy [89].

Two studies examined the relationship between preeclampsia and future retinopathy in women with type 1 diabetes. Sight-threatening deterioration of retinopathy was more common among Swedish women who had preeclampsia, compared to those who did not have preeclampsia (50% vs. 9%), at six months post-partum [90]. A later study in the Finnish cohort that was described in the preceding paragraph examined the risk of severe diabetic retinopathy [91]. Compared to women who had normotensive pregnancies, women who had preeclampsia were more likely to develop severe diabetic retinopathy (hazard ratio: 3.9 95% CI: 3.9, 1.3–11.3)after 16 years of follow-up [91]. Poor glycemic control likely contributed to this effect, as the strength of the association was attenuated after adjusting for HbA_{1c}in pregnancy (hazard ratio: 2.0, 95% CI: 0.6–6.8) [91].

Existing research suggests that preeclampsia is a risk factor for diabetic retinopathy and nephropathy among women with type 1 diabetes. Larger studies that can control for additional risk factors and examine the risk of other types of complications are needed. The mechanisms for increased rates of complications in women with a history of preeclampsia are not yet known. Women who develop preeclampsia may have more advanced disease and poorer glycemic control prior to pregnancy [23]. Genetic or environmental factors that contribute to preeclampsia could also increase the risk of diabetic complications later in life. Alternatively, preeclampsia may cause lasting damage that leads to diabetic complications years after pregnancy. If preeclampsia causes lasting damage, then new therapeutic targets for blood pressure, glycemic control, and other clinical indicators may be needed to prevent this damagein preeclamptic women with type 1 diabetes.

Conclusions

The high prevalence of preeclampsia among women with preexisting diabetes highlights the need for research examining predictive markers, pathophysiology, treatment and the long-term health implications of preeclampsia in this population. However, multicenter studies and years of recruitment are often needed to obtain large cohorts of pregnant women with type 1 or type 2 diabetes. Standardized criteria for preeclampsia diagnosis in women who have proteinuria prior to pregnancy are urgently needed.

More research is also needed to examine the possibility that GDM and preeclampsia share a common etiologic pathway. Many maladaptations to pregnancy are common to both conditions, suggesting that their pathophysiology may overlap. However, studies to date have not had the power to compare biomarkers and risk factors among women with preeclampsia alone, GDM alone and preeclampsia with GDM. A better understanding of the shared and separate pathophysiologies of these two conditions may help researchers and clinicians to optimize screening techniques and improve treatments for GDM and preeclampsia.

Large registry studiess how that preeclampsia is a risk factor for diabetes later in life. Additional studies are needed to quantify the risks of type 1 vs. type 2 diabetes. Researchers should also determine whether any observed increase in the risk of type 1 diabetes reflects new onset disease, or is due to preexisting disease that was never diagnosed. A few studies suggest that women with type 1 diabetes who have had preeclampsia are at increased risk for retinopathy and nephropathy later in life. These women may benefit from additional monitoring to prevent, detect and treat diabetic complications after pregnancy. However, larger studies that can control for additional risk factors, and studies examining other types of complications, are needed. Given the increasing prevalence of type 2 diabetes in pregnant women [92], future studies should also examine the relationship between preeclampsia and diabetic complications in women with type 2 diabetes.

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* Of importance

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Table 1

Risk of diabetes after a preeclamptic pregnancy

Study	Location	Postpartum Follow-up	Outcome	Pregnancy Outcome		
				Preeclampsia	Gestational Diabetes	Preeclampsia & Gestational Diabetes
Savitz *et al*., 2014 [88]	New York City	1 year	Hospitalization for Type 1 diabetes	OR: 1.8 (0.8, 3.8)[a]	OR: 40.4 (23.8-68.5)[b]	NA
			Hospitalization for Type 2 diabetes	OR: 2.0 (1.3, 3.2)[a]	OR: 22.6 (16.9, 30.4)[b]	NA
Engeland *et al*., 2011 [84]	Norway	Median: 3.7 years Range: 0 to 6 years	Risk of getting dispensed drugs for diabetes	RR: 3.0 (2.4, 3.6)	RR: 41 (35, 47)	RR: 79 (58, 108)
Feig *et al*., 2013 [85]	Ontario, Canada	Range: 3 months to 16.5 years	Diagnosis of diabetes	HR: 2.1 (2.0, 2.2)	HR: 12.8 (12.4, 13.1)	HR: 15.8 (14.5, 17.1)
Mannisto *et al*., 2013 [87]	Finland	Mean: 39 years Range: 3.0 to 43.6 years	ICD code for diabetes	HR: 1.4 (0.9, 2.2)[a]	NA	NA
Libby *et al*., 2007 [86]	Dundee, Scotland	Median: ≈46 years	Type 2 diabetes	OR: 1.4 (1.1, 1.8)[a]	NA	NA

Values are presented as odds ratios (OR), relative risk (RR) or hazard ratios (HR) and 95% confidence intervals, adjusted for confounding variables included in the study. Not applicable (NA) indicates that the group was not included in the study.

[a] Includes women with concomitant gestational diabetes

[b] Includes women with concomitant preeclampsia