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ORIGINAL ARTICLE

Pre-eclampsia and pregnancy-induced hypertension are associated with severe diabetic retinopathy in type 1 diabetes later in life

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Abstract To investigate whether pre-eclampsia (PE) or pregnancy-induced hypertension (PIH) predicts the development of severe diabetic retinopathy (SDR) in type 1 diabetes. Altogether, 203 women with type 1 diabetes who were followed during pregnancy were re-examined within the Finnish Diabetic Nephropathy Study. After excluding patients with pre-pregnancy hypertension and those who had had laser treatment or whose retinopathy was graded as proliferative at the index pregnancy, 158 were prospectively studied. As a surrogate marker for SDR, retinal laser photocoagulation was used. The time from pregnancy to SDR ($N = 21$) or follow-up was 16 years (interquartile range, 11–19). HbA_{1c} was repeatedly measured both during pregnancy and follow-up. Women with prior PE (26 % vs. 6 %, $P = 0.003$) or PIH (24 % vs. 6 %, $P = 0.008$) had more often incident SDR during follow-up compared to those with normotensive pregnancy. The hazard ratios (HR) remained associated with the progression to SDR after adjustment for duration of diabetes and diabetic nephropathy in a Cox regression analysis [PE: 3.5 (95 % CI 1.1–10.9); $P = 0.03$ and for PIH: 3.2 (1.1–9.8); $P = 0.04$]. The association between PIH and incident SDR did not change after inclusion of mean HbA_{1c}, measured during pregnancy (all 3 trimesters) and serial HbA_{1c} measurements during follow-up, 3.5 (1.1–11.8; $P = 0.03$). However, in a similar model, the HR for PE was no more significant 2.0 (0.6–6.8; P = NS). The results suggest that women with type 1 diabetes and a hypertensive pregnancy have an increased risk of severe diabetic retinopathy later in life.

Keywords Diabetic retinopathy · Hypertensive pregnancy · Pre-eclampsia · Pregnancy-induced hypertension · Severe diabetic retinopathy · Type 1 diabetes

This work was done on behalf of the FinnDiane Study Group.

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Abbreviations

DN	Diabetic nephropathy
HR	Hazard ratio
PE	Pre-eclampsia
PIH	Pregnancy-induced hypertension
SDR	Severe diabetic retinopathy
T1D	Type 1 diabetes

Introduction

Hypertensive disorders are more common in diabetic than in non-diabetic pregnancies, and important causes of

maternal and fetal morbidity and mortality [1–3]. Pre-eclampsia and pregnancy-induced hypertension have been argued to differ in their pathogenesis, although both entities associate with vascular disease, such as the development of hypertension and metabolic syndrome, years after pregnancy [4]. Moreover, several studies have shown that women with a history of pre-eclampsia are at increased risk of cardiovascular morbidity and mortality later in life [5–7]. Interestingly, pre-eclampsia was also reported to predict end-stage renal disease in a large Norwegian population-based registry study [8]. However, only a few studies have assessed long-term effects of hypertensive disorders on late diabetic microvascular complications. We have earlier shown that pre-eclampsia is a risk factor for diabetic nephropathy in women with type 1 diabetes [9]. In contrast, pregnancy-induced hypertension was not associated with diabetic nephropathy. Whether hypertensive pregnancy is also a risk factor for diabetic retinopathy is unknown. The aim of this study was therefore to assess whether pre-eclampsia or pregnancy-induced hypertension predicts the development of severe diabetic retinopathy in women with type 1 diabetes later in life.

Research design and methods

Baseline (index pregnancy)

A total of 396 women with type 1 diabetes were followed throughout their pregnancy at the Helsinki University Central Hospital, Department of Obstetrics and Gynaecology, between 1988 and 1996. The patients visited the hospital starting at 6–10 weeks of pregnancy, at 2–6-week intervals throughout the pregnancy. They were advised to measure their blood glucose at home five times daily on two to three days per week in order to achieve good glycemic control defined as a HbA_{1c} <7.5 %. For this purpose, they were prescribed long-acting insulin, 1–3 times daily, and short-acting insulin at meals. Blood pressure was measured by a sphygmomanometer after a 10-min rest at each visit. Blood pressure was considered increased when diastolic blood pressure was repeatedly ≥90 mmHg or if it increased by a minimum of 15 mmHg during pregnancy. Urinary protein was measured by a dipstick method at each visit. If the dipstick repeatedly showed a + or a ++ result, the proteinuria (≥300 mg/24 h) was confirmed by a 24-h urine collection. Pre-eclampsia was defined as increased blood pressure combined with proteinuria after 20 weeks of pregnancy. Pregnancy-induced hypertension was defined as increased blood pressure without proteinuria [10, 11]. HbA_{1c} was measured each month throughout the pregnancy (Diamat; Bio-Rad Laboratories, Hercules, CA, USA). The first assessment during pregnancy was done at a median of 7 weeks of gestation (range, 7–14 weeks). The mid-pregnancy HbA_{1C} used was obtained closest to 22 weeks of gestation (range, 20–25 weeks), and the third measurement 2 weeks (range, 0–4 weeks) before delivery. The mean of 3 (1 per trimester) HbA_{1c} (6.6 ± 1.0 %) measurements during pregnancy was used in the analysis.

Follow-up study

The follow-up visit was part of the Finnish Diabetic Nephropathy (FinnDiane) Study, a nationwide, prospective, multicentre study founded to uncover the risk factors and mechanisms of diabetic complications. At follow-up complete data on 203, of the 396 patients followed during pregnancy, were available. No clear differences were found in the baseline clinical characteristics of patients who participated in the follow-up study and those who did not as earlier described [9]. Altogether, 158 patients were included in the analysis after excluding patients with pre-pregnancy hypertension ($N = 23$) and those who had had laser treatment or whose retinopathy was graded as proliferative at the index pregnancy ($N = 22$) based on the ETDRS (early treatment diabetic retinopathy study) score from fundus photographs [12, 13]. At follow-up, a history of laser photocoagulation of the retina was used as a surrogate marker for severe diabetic retinopathy (SDR) [14, 15]. The existence of laser photocoagulation during follow-up was verified from medical records until the end of year 2010. The median time from pregnancy to an event or follow-up was median 16 years (interquartile range, 11–19). During this period, 21 patients had retinal laser treatment for the first time. Although laser treatment was mostly due to proliferative diabetic retinopathy, two women with a normotensive pregnancy were treated for macular edema.

During follow-up, serial laboratory values of HbA_{1C} (8.5 ± 1.2 %) were obtained. The median number of HbA_{1C} measurements per patient during follow-up was 13 (interquartile range, 8–18). A strong correlation between the HbA_{1C} (8.7 ± 1.5 %) at the follow-up visit and the serial HbA_{1C} (8.5 ± 1.2 %) measurements during follow-up was observed, $r = 0.73$, $P < 0.001$. Renal status was based on urinary albumin excretion rate (UAER) in at least two out of three consecutive timed (either 24 h or overnight) urine collections, such that microalbuminuria was defined by a UAER of 20–200 μg/min, macroalbuminuria by a UAER >200 μg/min, and normoalbuminuria by a UAER <20 μg/min. Patients on dialysis or those who had gained a kidney transplant were considered to have end-stage renal disease (ESRD). Diabetic nephropathy status was used in the multivariate analysis as a categorical variable divided into four categories: normo-, micro-, macroalbuminuria, and ESRD [16]. Estimated glomerular

filtration rate was calculated using the Modification of Diet in Renal Disease four-variable equation [17]. The study was approved by ethics committees of participating centers and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each patient.

All analyses were performed with SPSS 18.0.1 (SPSS, Chicago, IL, USA). Baseline characteristics were presented as mean ± SD for normally distributed variables and median with interquartile range for non-normally distributed values, and percentages. For categorical values, the χ^2 test was used. Normally distributed variables were tested with the Student's *t* test and non-normally distributed with the Mann–Whitney *U* test. Longitudinal data were analyzed with Kaplan–Meier survival curves with log-rank tests and Cox proportional hazard survival regression with results as hazard ratio (HR) and 95 % CI. Survival curves were drawn by GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA).

Results

During the index pregnancy, 97 women were normotensive, 32 had pre-eclampsia, and 29 had pregnancy-induced hypertension. Clinical characteristics are shown in Table 1. Both women with pre-eclampsia and pregnancy-induced hypertension were younger at the time of pregnancy compared to those with a normal blood pressure during pregnancy. Similarly, the gestational age and birth weight of the fetus at delivery were lower in patients with pre-eclampsia. Moreover, women with a history of pre-eclampsia had a higher HbA_{1c} than those with a normotensive pregnancy. No difference in HbA_{1c} was observed during each trimester between women with pregnancy-induced hypertension and normal blood pressure during pregnancy.

During follow-up, women with a history of pre-eclampsia more often developed severe diabetic retinopathy than

Table 1 Characteristics of patients by status during pregnancy and at follow-up

	Normotensive pregnancy ($N = 97$)	Pre-eclampsia ($N = 32$)	Pregnancy-induced hypertension ($N = 29$)
Baseline			
Age (years)	30.3 ± 4.8	27.7 ± 4.1[b]	28.1 ± 5.1[b]
Duration of diabetes (years)	12.0 ± 7.9	14.6 ± 6.3	12.8 ± 7.7
BMI (kg/m^2)	22.6 ± 3.0	22.2 ± 2.2	23.7 ± 3.3
Gestational age at delivery (wk)	37.5 ± 1.6	36.3 ± 1.4[a]	37.2 ± 1.2
Birth weight *Z* score (SD)	1.6 ± 1.7	1.4 ± 2.0	2.0 ± 1.5
Birth weight (g)	3.863 ± 732	3.520 ± 848[b]	3.930 ± 450
HbA_{1c} I trimester (%)	7.4 ± 1.3	8.0 ± 1.5[b]	7.2 ± 1.4
HbA_{1c} II trimester (%)	6.3 ± 0.9	6.8 ± 0.9[b]	6.4 ± 1.0
HbA_{1c} III trimester (%)	6.6 ± 0.9	7.0 ± 1.0[b]	6.8 ± 1.1
Follow-up			
Age (years)	42.1 ± 6.5	36.9 ± 5.7[b]	40.0 ± 5.5
Duration of diabetes (years)	24.0 ± 8.5	24.3 ± 7.5	24.6 ± 9.1
BMI (kg/m^2)	24.8 ± 4.5	23.9 ± 2.9	25.2 ± 3.3
Waist-to-hip ratio	0.84 ± 0.06	0.85 ± 0.06	0.84 ± 0.05
Systolic blood pressure (mmHg)	129 ± 15	132 ± 15	130 ± 14
Diastolic blood pressure (mmHg)	76 ± 10	81 ± 8[b]	79 ± 14
Total cholesterol (mmol/l)	4.7 ± 0.8	4.5 ± 0.7	4.8 ± 0.8
HDL cholesterol (mmol/l)	1.8 ± 0.5	1.9 ± 0.4	1.9 ± 0.5
Triglycerides (mmol/l)	1.0 (0.8–1.2)	1.0 (0.8–1.1)	1.0 (0.9–1.1)
Serial HbA1c (%)[c]	8.5 ± 1.1	8.9 ± 1.4	8.3 ± 1.1
Insulin/Weight (IU/kg)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Estimated glomerular filtration rate (mL/min/1.73m^2)	108 ± 19	94 ± 27b	111 ± 27
Insulin pump treatment (%)	6	3	10
Ever smokers (%)	53	42	45
Anti-hypertensive treatment (%)	9	33b	41a
Laser-treated retinopathy (%)	6	26b	24b

Data are mean ± SD, median (interquartile range), or percent

[a] $P < 0.001$ and [b] $P < 0.05$ versus normotensive pregnancy. [c] Serial laboratory values of HbA_{1c} obtained during follow-up ($N = 13$ [8–18])

those with a normotensive pregnancy (26 % vs. 6 %; $P = 0.003$). A similar finding was observed for pregnancy-induced hypertension compared to pregnancies with a normal blood pressure (24 % vs 6 %; $P = 0.008$). Furthermore, 33 % with pre-eclampsia ($P = 0.001$) and 41 % with pregnancy-induced hypertension ($P < 0.001$) were on anti-hypertensive treatment during follow-up compared to 9 % in patients with normotensive pregnancy. No difference in smoking was observed between the groups.

Kaplan–Meier survival curves revealed a higher incidence of incident severe diabetic retinopathy during follow-up in women with a history of pre-eclampsia or pregnancy-induced hypertension compared to normal blood pressure during pregnancy (Fig. 1). Pre-eclampsia remained associated with the progression to SDR during follow-up after adjustment for duration of diabetes and diabetic nephropathy status in a multivariate Cox regression analysis [HR 3.5, 95 % CI (1.1–10.9); $P = 0.03$] (Table 2). Similarly, the HR for pregnancy-induced hypertension as a predictor for severe diabetic retinopathy was 3.2 (1.1–9.8; $P = 0.04$). The association between pre-eclampsia and incident severe diabetic retinopathy decreased after inclusion of mean HbA_{1c}, measured during pregnancy (all 3 trimesters) and serial HbA_{1c} measurements during follow-up, in the model 2.0 (0.6–6.8; P = NS). However, in a similar model, the HR for pregnancy-induced hypertension was still significant 3.5 (1.1–11.8; $P = 0.03$). The results did not change either for pre-eclampsia [HR, 2.8 95 % CI (0.7–10.6); $P = 0.14$] or pregnancy-induced hypertension [HR, 4.2 95 % CI (1.0–17.8); $P = 0.045$] after inclusion of anti-hypertensive treatment in model 3 (Table 3). The same observation was made if anti-hypertensive was replaced by angiotensin converting receptor inhibitor/angiotensin receptor blocker treatment (data not shown).

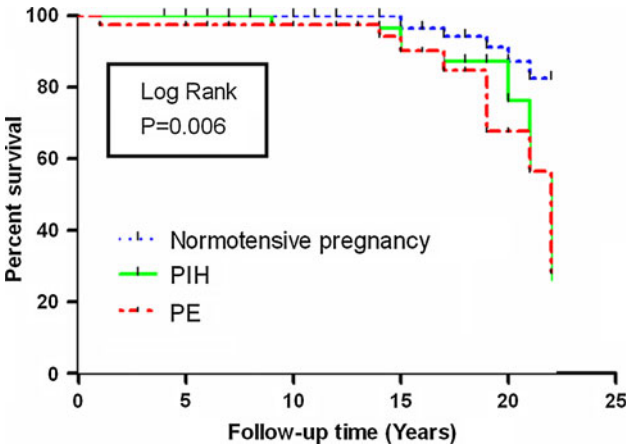

Fig. 1 Kaplan–Meier survival curves for laser-treated retinopathy ($N = 21$) during follow-up by pregnancy outcome. Follow-up time 16 years (interquartile range, 11–19). Normotensive pregnancy ($N = 97$), PE = pre-eclampsia ($N = 32$), PIH = Pregnancy-induced hypertension ($N = 29$)

Notably, we could not observe any association between the change in HbA_{1c} during pregnancy and severe diabetic retinopathy later in life after including duration of diabetes, diabetic nephropathy status, and the cumulative values of HbA_{1c} during pregnancy and follow-up as covariates in the Cox model [1.03 (0.7–1.4); $P = 0.87$].

Poor glycemic control during pregnancy was observed in women who developed incident severe diabetic retinopathy (Table 3). No difference in age or duration of diabetes was seen. The level of mean serial HbA_{1c} (8.8 ± 0.8 % vs. 7.6 ± 0.8 %; $P < 0.001$) during follow-up was increased in women with incident severe diabetic retinopathy.

Discussion

The main result of this study was the observation that women with type 1 diabetes and a hypertensive pregnancy developed severe diabetic retinopathy during follow-up more often than women with a normotensive pregnancy. The association between a hypertensive pregnancy and

Table 2 Cox regression analysis to assess the predictive value of pre-eclampsia and pregnancy-induced hypertension for progression to severe diabetic retinopathy during follow-up

	Pre-eclampsia HR (95 % CI); P value	Pregnancy-induced hypertension HR (95 % CI); P value
Model 1	3.9 (1.3–11.3); $P = 0.02$	3.5 (1.2–10.5); $P = 0.03$
Model 2	3.5 (1.1–10.9); $P = 0.03$	3.2 (1.1–9.8); $P = 0.04$
Model 3	2.0 (0.6–6.8); P = NS	3.5 (1.1–11.8); $P = 0.03$

Results are presented as hazard ratios (HR) and 95 % CI

Model 1 adjusted for duration of diabetes

Model 2 adjusted for duration of diabetes and diabetic nephropathy status

Model 3 adjusted for duration of diabetes, diabetic nephropathy status, and mean HbA_{1c}, measured during pregnancy (all 3 trimesters), and serial HbA_{1c} measurements during follow-up

Table 3 Clinical characteristics of the patients at index pregnancy by laser-treated retinopathy during follow-up ($N = 158$)

	No laser-treated retinopathy ($n = 137$)	Laser-treated retinopathy ($n = 21$)
Index pregnancy		
Age (years)	29.6 ± 4.8	27.8 ± 5.4
Diabetes duration (years)	12.3 ± 7.6	15.1 ± 7.0
BMI (kg/m^2)	22.6 ± 2.7	24.0 ± 3.8[b]
Gestational age at delivery (wk)	37.3 ± 1.5	36.8 ± 1.1
Birth weight *Z* score (SD)	1.6 ± 1.6	1.6 ± 2.1
Birth weight (g)	3.822 ± 719	3.720 ± 764
HbA_{1c} I trimester (%)	7.2 ± 1.2	8.8 ± 1.3[a]
HbA_{1c} II trimester (%)	6.3 ± 0.9	7.0 ± 1.1[a]
HbA_{1c} III trimester (%)	6.6 ± 0.9	7.3 ± 0.9[b]
Pre-eclampsia (%)	16	38[b]
Pregnancy-induced hypertension (%)	16	33[b]
Non-hypertensive pregnancy (%)	68	29[b]

Data are mean ± SD or percent. [a] $P < 0.001$ and [b] $P < 0.05$ versus no laser-treated retinopathy

severe diabetic retinopathy later in life was independent of glycemic control in pregnancy-induced hypertension but not pre-eclampsia.

Earlier studies have reported that women with a history of pre-eclampsia are at an increased risk for hypertension, cardiovascular disease, and renal disease [4–9]. We showed that pre-eclampsia but not pregnancy-induced hypertension was associated with diabetic nephropathy in patients with type 1 diabetes [9]. The results of the current study in turn indicate that both women with pre-eclampsia and pregnancy-induced hypertension are at increased risk for sight-threatening diabetic retinopathy. As pregnancy-induced hypertension is by definition not associated with signs of renal dysfunction, it may not be surprising that the diabetic nephropathy status did not affect the relationships between pregnancy-induced hypertension and severe diabetic retinopathy. Thus, our results support the earlier hypothesis that pre-eclampsia and pregnancy-induced hypertension are different disease entities that may be of clinical relevance [2].

The diagnosis of severe diabetic retinopathy was based on the history of retinal laser treatment rather than the examination of fundus photographs. Notably, laser treatment is the standard care for both severe macular edema as well as proliferative retinopathy. In our cohort, proliferative retinopathy was the indication for laser treatment in all but two women (macular edema). However, as these women had a history of normal blood pressure during pregnancy, it is unlikely that this diluted the findings.

A number of risk factors for diabetic retinopathy have been characterized in patients with type 1 diabetes such as hypertension, male sex, proteinuria, BMI, duration of diabetes, and HbA_{1c} [18]. In our cohort, a large number of the women with de novo hypertension during pregnancy had hypertension also during follow-up that is in line with earlier findings [4, 6]. However, pregnancy-induced hypertension was independently associated with severe diabetic retinopathy even after correcting for anti-hypertensive treatment. Notably, the results were also independent of diabetic nephropathy. HbA_{1c} was increased during pregnancy in patients with pre-eclampsia, but not pregnancy-induced hypertension, compared to women with normal hypertension. Pregnancy-induced hypertension was still predictive for severe diabetic retinopathy after including the serial HbA_{1c} values in the multivariate model although pre-eclampsia was not. It has earlier been shown that glycemic control during pregnancy is associated with pre-eclampsia but not pregnancy-induced hypertension. However, an improvement in glycemic control during pregnancy did not alter the risk of pre-eclampsia [2, 19]. Similarly, a decrease in HbA_{1c} during pregnancy was not independently associated with a reduced risk of severe diabetic retinopathy later in life.

The finding that women with either a history of pre-eclampsia or pregnancy-induced hypertension had severe diabetic retinopathy more often later in life, whereas diabetic nephropathy was only increased in women with pre-eclampsia is intriguing. The reason for the finding cannot conclusively be answered by this observational study. Notably, the pathophysiology of pre-eclampsia and pregnancy-induced hypertension is incompletely understood. Maternal factors in pre-eclampsia (genetic, constitutional, and environmental) and related effects (chronic inflammation, dyslipidemia, insulin resistance, endothelial dysfunction, and oxidative stress) are also associated with increased risk for cardiovascular disease in later life [20]. Therefore, it is possible that chronic inflammation, endothelial dysfunction, and oxidative stress seen in both PE and diabetic nephropathy are required for the development of kidney disease in these women, whereas features of the metabolic syndrome in turn might be more important risk factors in those with pregnancy-induced hypertension [3, 18]. It may well be that especially hypertension shown to be a strong risk factor for diabetic retinopathy is a key risk factor severe diabetic retinopathy later in life in women with a history of pregnancy-induced hypertension. Another possible hypothesis is that pre-eclampsia and diabetic nephropathy share a genetic background that differs from that of pregnancy-induced hypertension [21]. Furthermore, chronic hyperglycemia is most likely involved, causing vascular damage through a number of mechanisms,

although pregnancy-induced hypertension predicted severe diabetic retinopathy independently of HbA_{1c} probably related to intermediate cardiovascular risk factors that have a gestational expression [22].

Diabetic retinopathy may progress during pregnancy in patients with type 1 diabetes. Somewhat conflicting studies report an increase in retinopathy for 17–70 % of patients [23, 24]. Diabetes duration, poor glycemic control, and increased blood pressure have been shown to increase the risk [25]. The definitive mechanism behind this phenomenon is unclear, although endothelial and inflammatory markers have been reported to be increased in patients with type 1 diabetes and progression of retinopathy status during pregnancy [13].

Although pregnancy *per se* seems to cause progression in diabetic retinopathy, only a few studies have investigated the role of pregnancy on long-term diabetic complications in patients with type 1 diabetes although de novo hypertension during pregnancy is more common in this patient group [26]. Pregnancy itself has not been reported to worsen diabetic microvascular complications later in life [27–29]. However, in a Swedish study, patients with pre-eclampsia suffered from a deterioration of retinopathy 6 months after the pregnancy compared to women without pre-eclampsia [30]. In our cohort, patients with pre-eclampsia and pregnancy-induced hypertension were analyzed separately and followed for 16 years. Severe diabetic retinopathy was more common in both groups compared to women with a history of normal blood pressure during pregnancy.

The pathophysiology of pregnancy-induced hypertension is largely unknown. However, insulin resistance has been suggested to be part of the process. It might also be secondary to other disorders, such as endocrine disorders, or renal artery stenosis. Most likely pregnancy-induced hypertension is often a first sign of essential hypertension, analogous to gestational diabetes and the development of type 2 diabetes later in life [26, 31].

To predict diabetic complications has despite intensive research turned out to be an extremely difficult task. Pregnancy may partly serve as window into the future health of women with type 1 diabetes. Our findings suggest that women with type 1 diabetes and a hypertensive pregnancy have an increased risk of severe diabetic retinopathy later in life.

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Conflict of interest PHG has gained lecture fees from Eli Lilly, Boehringer Ingelheim, Novartis, Genzyme, MSD, and Novo Nordisk, and he is an advisory board member of Boehringer Ingelheim, Novartis, and Cebix. The other authors declare that there is no duality of interest associated with this manuscript.

References

1. Ewers IM, de Valk HW, Visser GHA (2004) Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. Br Med J 328:915–921
2. Hiilesmaa V, Suhonen L, Teramo K (2000) Glycaemic control is associated with pre-eclampsia but not with pregnancy-induced hypertension in women with type I diabetes mellitus. Diabetologia 43:1534–1539
3. Redman CW, Sargent IL (2005) Latest advances in understanding preeclampsia. Science 308:1592–1594
4. Pouta A, Hartikainen AL, Sovio U, Gissler M, Laitinen J, McCarthy MI, Ruokonen A, Elliott P, Järvelin MR (2004) Manifestations of metabolic syndrome after hypertensive pregnancy. Hypertension 43:825–831
5. Irgens HU, Reisaeter L, Irgens LM, Lie RT (2001) Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. Br Med J 323:1213–1217
6. Hannaford P, Ferry S, Hirsch S (1997) Cardiovascular sequelae of toxaemia of pregnancy. Heart 77:154–158
7. Haukkamaa L, Salminen M, Laivuori H, Leinonen H, Hiilesmaa V, Kaaja R (2004) Risk for subsequent coronary artery disease after preeclampsia. Am J Cardiol 93:805–808
8. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM (2008) Preeclampsia and the risk of end-stage renal disease. N Engl J Med 359:800–809
9. Gordin D, Hiilesmaa V, Fagerudd J, Rönnback M, Forsblom C, Kaaja R, Teramo K, Groop PH, FinnDiane Study Group (2007) Pre-eclampsia, but not pregnancy-induced hypertension is a risk factor for diabetic nephropathy in type 1 diabetic women. Diabetologia 50:516–522
10. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000) Report of the national high blood pressure education program working group on high blood pressure in pregnancy. Am J Obst Gynecol 83:S1–S22
11. Levine RJ, Ewell MG, Hauth JC, Curet LB, Catalano PM, Morris CD, Choudhary G, Sibai BM (2000) Should the definition of preeclampsia include a rise in diastolic blood pressure of Q15 mm Hg to a level <90 mm Hg in association with proteinuria? Am J Obst Gynecol 183:787–792
12. Early Treatment Diabetic Retinopathy Study Research Group (1991) Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Ophthalmology 98:823–833
13. Loukovaara S, Immonen I, Koistinen R, Hiilesmaa V, Kaaja R (2005) Inflammatory markers and retinopathy in pregnancies complicated with type 1 diabetes. Eye Lond 19:422–430
14. Grassi MA, Mazzulla DA, Knudtson MD, Huang WW, Lee KE, Klein BE, Nicolae DL, Klein R (2009) Patient self-report of prior laser treatment reliably indicates presence of severe diabetic retinopathy. Am J Ophthalmol 147:501–504
15. Kytö JP, Harjutsalo V, Forsblom C, Hietala K, Summanen PA, Groop PH, on behalf of the FinnDiane Study Group (2011) Decline in the cumulative incidence of severe diabetic retinopathy in patients with type 1 diabetes. Diabetes Care 3: 2005–2007

16. Groop PH, Thomas MC, Moran JL, Wadèn J, Thorn LM, Mäkinen VP, Rosengård-Bärlund M, Saraheimo M, Hietala K, Heikkilä O, Forsblom C, FinnDiane Study Group (2009) The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 58:1651–1658
17. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology Collaboration (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145:247–254
18. Klein R, Knudtson MD, Lee KE, Gagnon R, Klein BE (2008) The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 115:1859–1868
19. Holmes VA, Young IS, Patterson CC, Pearson DW, Walker JD, Maresh MJ, McCance DR, Diabetes and Pre-eclampsia Intervention Trial Study Group (2011) Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. Diabetes Care 34:1683–1688
20. Lain KY, Roberts JM (2002) Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA 287: 3183–3186
21. Arngrimsson R, Bjornsson S, Gersson RT, Bjornsson II, Walker JJ, Snaedal G (1990) Genetic and familial predisposition to eclampsia and preeclampsia in a defined population. Br J Obstet Gynaecol 97:131–140
22. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. Nature 414:813–820
23. Klein BE, Moss SE, Klein R (1990) Effect of pregnancy on progression of diabetic retinopathy. Diabetes Care 13:34–40
24. Dibble CM, Kochenour NK, Worley RJ, Tyler FH, Swartz M (1982) Effect of pregnancy on diabetic retinopathy. Obstet Gynecol 59:699–704
25. Chew EY, Mills JL, Metzger BE, Remaley NA, Jovanovic-Peterson L, Knopp RH, Conley M, Rand L, Simpson JL, Holmes LB (1995) Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. Diabetes Care 18:631–637
26. Colatrella A, Loguercio V, Mattei L, Trappolini M, Festa C, Stoppo M, Napoli A (2010) Hypertension in diabetic pregnancy: impact and long-term outlook. Best Pract Res Clin Endocrinol Metab 24:635–651
27. Diabetes Control and Complications Trial Research Group (2000) Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes Care 23:1084–1091
28. Vérier-Mine O, Chaturvedi N, Webb D, Fuller JH (2005) Is pregnancy a risk factor for microvascular complications? The EURODIAB Prospective Complications Study. Diabet Med 22:1503–1509
29. Kaaja R, Sjöberg L, Hellsted T, Immonen I, Sane T, Teramo K (1996) Long-term effects of pregnancy on diabetic complications. Diabet Med 13:165–169
30. Lövestam-Adrian M, Agardh CD, Aberg A, Agardh E (1997) Pre-eclampsia is a potent risk factor for deterioration of retinopathy during pregnancy in Type 1 diabetic patients. Diabet Med 14: 1059–1065
31. Lindheimer MD, Taler SJ, Cunningham FG (2010) Hypertension in pregnancy. J Am Soc Hypertens 4:68–78