0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism
Copyright © 1996 by The Endocrine Society
Vol. 81, No. 8
Printed in U.S.A.

Hyperinsulinemia 17 Years after Preeclamptic First Pregnancy*

HANNELE LAIVUORI, MATTI J. TIKKANEN, AND OLAVI YLIKORKALA

Department of Obstetrics and Gynecology and Medicine, University Central Hospital of Helsinki, Helsinki, Finland

ABSTRACT

Insulin resistance syndrome predisposes to occlusive vascular disorders in nonpregnant subjects. Because preeclampsia, representing a pregnancy-specific occlusive vascular disorder, is known to be accompanied by metabolic changes similar to those in insulin resistance syndrome, we compared carbohydrate and lipid metabolism in 22 women who had had a preeclamptic first pregnancy and in 22 control women who had had normotensive first pregnancy, both, on the average, 17.0 ± 0.7 yr earlier. The study groups were comparable in regard to body mass index at the follow-up study. Women with prior preeclampsia were normoglycemic (baseline, 3 h oral glucose tolerance), but showed a significant hyperinsulinemia, as seen from elevated immunoreactive insulin (IRI) levels at the baseline (mean ± SE, 7.3 ± 0.6 *vs.* 5.5 ± 0.5 mU/L; $P < 0.03$), after 1 h (45.7 ± 5.5 *vs.* 35.6 ± 3.5 mU/L; $P = 0.13$), after 2 h (32.4 ± 4.1 *vs.* 23.8 ± 2.3 mU/L; $P = 0.08$), and after 3 h (10.1 ± 1.4 *vs.* 6.4 ± 0.6 mU/L; $P = 0.02$). The area under the IRI curve was larger in the women with prior preeclampsia (86.8 ± 9.1 *vs.* 65.4 ± 5.2 mU/h·L; $P = 0.05$). The serum levels of total cholesterol, high density lipoprotein (HDL) cholesterol (with its subfractions HDL_2 and HDL_3), low density lipoprotein cholesterol, triglyceride, or uric acid did not differ significantly between the study groups. In women with prior preeclampsia, the area under the IRI curve was negatively related to HDL_2 cholesterol, but positively related to triglyceride and systolic blood pressure. We conclude that a history of preeclampsia is associated with mild hyperinsulinemia in nonpregnant women. (*J Clin Endocrinol Metab* **81:** 2908–2911, 1996)

WE HAVE RECENTLY demonstrated that women with preeclampsia and pregnancy-induced hypertension (PIH) display hyperinsulinemia, hypertriglyceridemia, and low high density lipoprotein (HDL) cholesterol (1). These women appear to have a form of insulin resistance syndrome (2–4) in the absence of recognized gestational diabetes. We reasoned that if the features of the insulin resistance syndrome were only transiently related to pregnancy, they would be absent years later. Conversely, persistence of these features would suggest that a more causal link between preeclampsia and insulin resistance syndrome could exist. To determine whether this association persisted, we compared carbohydrate metabolism and lipid profiles in women who had had preeclampsia many years earlier to those who had not to better understand the long term natural history of this disorder of pregnancy.

Subjects and Methods

With the permission of the local ethics committee, we studied 22 women who had given birth to a first child between 1976 to 1978 (Table 1). All women had been healthy before their first pregnancy, but 20 developed preeclampsia during their 32–38 weeks of pregnancy (blood pressure constantly >160/110 mm Hg; proteinuria, >0.3 g/24 h) (5). An additional woman experienced eclamptic seizures at 29 weeks, and 1 at 41 weeks. All preeclamptic/eclamptic women delivered healthy babies at 29–41 weeks vaginally (n = 6) or abdominally (n = 16). Six weeks postpartum, each woman was normotensive (blood pressure <125/80 mm Hg), and no protein was excreted into the urine. These women formed the preeclamptic group. For each patient we selected an age-matched control woman who had given birth to a first child at the same time (±3–4 months) after an entirely normotensive pregnancy at the same hospital (Table 1).

Protocol

The study subjects were first interviewed by telephone. Then, the patient and her control were invited to the research center during the same phase of their menstrual cycles. The cycle phase could not be taken into account in nine women, because six had been hysterectomized (four patients and two controls) and three (two patients and one control) did not menstruate due to the use of a levonorgestrel-releasing intrauterine device (IUD; Levonova, Leiras, Finland). In addition two women (one patient and one control) received estrogen-progestin replacement therapy [per woman transdermal estrogen (50 μg/24 h) plus a 10-day course of medroxyprogesterone acetate (10 mg/day), per woman oral estradiol valerate (2 mg/day), plus a 10-day course of medroxyprogesterone acetate (10 mg/day)], and one woman in the control group used lynestrenol (0.5 mg daily) for progestin-only contraception. The women came to the research center at 0800 h after an overnight fast. After the physical examination (height, weight, and blood pressure measurements), blood was drawn for measurement of uric acid, lipids, baseline blood glucose, and serum immunoreactive insulin (IRI) concentrations. Thereafter, a 3-h oral glucose tolerance test (75.0 g glucose) was started.

Laboratory methods

Whole blood glucose was measured with the enzymatic-amperometric method (ESAT 6660 analyzer, Eppendorf-Nelheler-Hinz, Hamburg, Germany), whereas sera for IRI assessment were stored frozen (−20 C) until assayed in the same batch of the assay by RIA (Phadeseph Insulin RIA kit, Kabi Pharmacia, Uppsala, Sweden). The antibody assay shows less than 0.18% cross-reactivity with C peptide, but 41% cross-reactivity with human proinsulin. Basal sera were assayed for uric acid with enzymatic colorimetric test (6) and for cholesterol using an enzymatic method with a commercial kit (Boehringer Mannheim, Mannheim, Germany) (7). HDL cholesterol was measured after precipitation of very low

Received June 6, 1995. Revision received October 25, 1995. Rerevision received February 22, 1996. Accepted March 15, 1996.

Address all correspondence and requests for reprints to: Hannele Laivuori, M.D., Department of Obstetrics and Gynecology, University Central Hospital of Helsinki, Haartmaninkatu 2, FIN-00290 Helsinki, Finland.

* This work was supported by grants from the Finnish Academy of Science, the Obstetric and Gynecologic Research Foundation, and the Clinical Research Institute of the Helsinki University Central Hospital.

Downloaded from https://academic.oup.com/jcem/article/81/8/2908/2875655 by guest on 16 August 2022

TABLE 1. Characteristics of study population

	Women with prior preeclampsia or eclampsia (n = 22)	Control women (n = 22)	*P* value
In association with first pregnancy			
Age (yr)	24.8 ± 0.9	25.0 ± 0.9	NS
Prepregnancy body mass index (kg/m^2)	20.7 ± 0.6	19.4 ± 0.3	NS
Gestational week at delivery	36.2 ± 0.5	40.1 ± 0.4	0.0001
Type of delivery			0.0001
Vaginal	6	21	
Cesarean section	16	1	
Infants birth wt (g)	2191 ± 117	3503 ± 74	0.0001
At reexamination			
Age (yr)	41.8 ± 0.9	41.8 ± 0.9	NS
Yr since delivery	16.9 ± 0.1	17.0 ± 0.1	NS
Subsequent full-term pregnancies/women	21/15	27/19	NS
Body mass index (kg/m^2)	23.3 ± 0.8	21.9 ± 0.4	NS
Change in body mass index since prepregnancy state (kg/m^2)	2.3 ± 0.7	2.3 ± 0.4	NS
Smoking	3	5	NS
Systolic blood pressure (mm Hg)	127 ± 3	116 ± 2	0.004
Diastolic blood pressure (mm Hg)	82 ± 2	75 ± 1	0.01

Values are the mean ± SE.

density lipoprotein and low density lipoprotein (LDL) with heparin and manganese chloride (8). Separation of the HDL subfractions was accomplished by adding dextran sulfate to the plasma supernatant to precipitate HDL_2 and HDL_3 (9). LDL cholesterol was calculated according to the Friedewald formula (10). The triglyceride concentrations were analyzed enzymatically (11).

Statistical analyses

The areas under the IRI and glucose curves (AUCs) were calculated according to the method described by Matthews *et al.* (12). Data are expressed as the mean ± SE and compared with the Statview II program (Abacus Concepts, Berkeley, CA) by unpaired Student's *t* test and contingency table analysis for classified data. As serum triglyceride levels showed skewed distributions, statistical analyses of these data were carried out after logarithmic transformation. Linear and multiple regression analyses were used to assess the relationship between metabolic parameters.

Results

With the exception of preeclampsia (or eclampsia in two women), the study groups were comparable at the time of the first pregnancy. Preeclamptic women gave birth to lighter infants and were delivered more often by cesarean section than did the control women (Table 1).

On the average, the women were restudied 17.0 ± 0.7 yr after their first pregnancy (Table 1). In the meantime, 15 women in the patient group had given birth to 21 infants. Of the second pregnancies (n = 15), 5 (33%) had been complicated by preeclampsia, and 4 (27%) by PIH. In their third pregnancies (n = 4), 2 developed preeclampsia, and in their fourth pregnancies (n = 2), 1 was hypertensive. In the control group, 19 women had given birth 27 times, and none had developed preeclampsia or PIH.

At reexamination, the two groups were comparable with regard to body mass index (BMI) and any change in it since the first pregnancy, but both mean systolic and diastolic blood pressures were higher in the preeclamptic women than those in the control group (Table 1). Two women in the preeclamptic group were hypertensive (blood pressure 155/100 and 150/100 mm Hg, respectively), but took no antihypertensive medication.

Blood glucose in the two groups at baseline and during the oral glucose tolerance test were comparable (Fig. 1). In the preeclamptic group, two women showed elevated 2-h glucose (8.6 and 7.8 mmol/L, respectively). IRI levels in the preeclamptic group were elevated at baseline (7.3 ± 0.6 *vs.* 5.5 ± 0.5 mU/L; $P = 0.03$), 1 h (45.7 *vs.* 35.6 mU/L; $P = 0.13$), 2 h (32.4 ± 4.1 *vs.* 23.8 ± 2.3 mU/L; $P = 0.08$), and 3 h (10.1 ± 1.4 *vs.* 6.4 ± 0.6 mU/L; $P = 0.02$; Fig. 1). The AUC for IRI was larger in the preeclamptic women than in the control group (86.8 ± 9.1 *vs.* 65.4 ± 5.2 mU/h·L; $P = 0.05$), whereas the AUCs for glucose were similar in the two groups (18.2 ± 0.6 *vs.* 17.6 ± 0.4 mmol/h·L). The elevated basal IRI levels in the preeclamptic group did not change even when IRI was adjusted for BMI.

Total cholesterol, LDL and HDL cholesterol, triglyceride, and uric acid concentrations did not differ significantly between the two groups (Table 2).

In the preeclamptic group, fasting IRI correlated positively with serum triglyceride ($r = 0.59$; $P < 0.01$), BMI ($r = 0.54$; $P < 0.01$), and systolic ($r = 0.69$; $P < 0.001$) and diastolic ($r = 0.47$; $P < 0.05$) blood pressures. All of these correlations remained significant even when analyzed in a multiple regression model. The AUC for IRI in the preeclamptic group correlated positively with serum triglyceride ($r = 0.57$; $P < 0.01$), BMI ($r = 0.49$; $P < 0.05$), and systolic blood pressure ($r = 0.53$; $P < 0.05$) and negatively with HDL_2 cholesterol ($r = -0.48$; $P < 0.05$). The AUC for IRI did not differ between those who had developed preeclampsia or hypertension in subsequent pregnancies and those who had not.

Hysterectomized women (n = 6) or women using a levonorgestrel-releasing IUD (n = 3), hormone replacement therapy (n = 2), or progestin-only contraception (n = 1) showed glucose, insulin, and lipid values within the range of the other women's values. In addition, when these women

Downloaded from https://academic.oup.com/jcem/article/81/8/2908/2875655 by guest on 16 August 2022

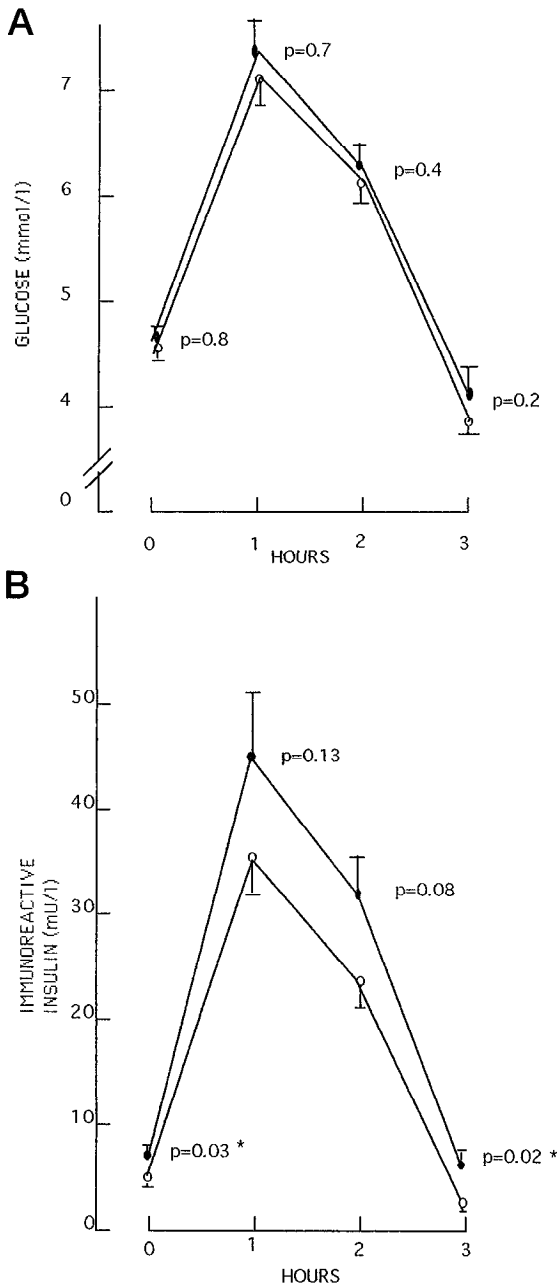

FIG. 1. Blood glucose and serum IRI (mean, SE) before and after intake of 75.0 g glucose in women with a history of preeclampsia or eclampsia (●) and in control women (○).

were excluded from the statistical analysis, the differences between the two groups did not change.

Discussion

We assessed the levels of IRI by RIA, using an antibody that cross-reacts with proinsulin. Therefore, it is theoretically possible that the elevated IRI levels in our study could also have reflected increased proinsulin levels. Both hyperinsulinemia and disproportionately increased proinsulin levels are reportedly associated with the insulin resistance syndrome (13). For the sake of brevity, we employ the common use of the term hyperinsulinemia in the text, although elevation of proinsulin levels cannot be excluded with the RIA method used by us and others (14, 15).

Our study showed that women were characterized by significantly elevated IRI levels but normoglycemia 17 yr after preeclamptic first pregnancy. These concomitant changes strongly imply that these patients have insulin resistance. This did not change even when IRI was adjusted for BMI, which is a significant determinant of the circulating insulin level (16–19). The elevated IRI levels were not explained by the potential confounding variables, such as menstrual cycle phase, hormonal contraception, or hormonal replacement therapy, because patients and controls were comparable in these regards. Moreover, no measurable changes in glucose-IRI or lipid balance were caused by the cycle phase (20–22), hormone-releasing IUD (23), progestin-only contraception (24), or hormonal replacement therapy in menopausal women (25–27). This was also found in our data, as hysterectomized women or women using exogenous hormones had glucose, IRI, and lipid values that fell within the range of the same variables in the other subjects. Although basal IRI concentrations or the IRI AUC are reasonable indicators of insulin resistance (15), insulin resistance could be more rigorously quantified by employing the euglycemic hyperinsulinemic clamp technique (28).

In the preeclamptic group, the magnitude of hyperinsulinemia (and thus, perhaps, insulin resistance) correlated negatively with HDL cholesterol, but positively with triglyceride and systolic and diastolic blood pressures. These relationships are typical of the insulin resistance syndrome (2–4). We do not know whether hyperinsulinemia in our patients is a consequence of previous preeclampsia or is an inherited feature, but the observation that the metabolic features in hypertensive pregnancies are similar to those in the insulin resistance syndrome supports the latter supposition (1). We can further speculate that hyperinsulinemia would be more aggravated if our study subjects could be studied between 50–60 yr of age. The etiology of preeclampsia is unknown, and our data may suggest that insulin resistance could be a factor in it. If this were true, preeclampsia should probably have reoccurred in subsequent pregnancies. Our data lend some support to this speculation; 9 of 15 women (60%) in the patient group were preeclamptic or hypertensive during their second pregnancies, in contrast to none in the control group. Yet, large series of patients must be studied before our data on hyperinsulinemia can be used in the treatment or follow-up of these patients.

The impact of prior preeclampsia on the future risk of hypertension is controversial (29–33). Most researchers agree that acute true preeclampsia does not predispose to subsequent hypertension (30–32), whereas the others, who had followed preeclamptic subjects as long as we did, found elevated blood pressure 10–20 yr after preeclampsia (29, 33). Our study subjects with an acute preeclamptic first pregnancy had a higher mean blood pressure than our control subjects, although only two of the patients were actually hypertensive. It was also noteworthy that systolic and diastolic blood pressures and the levels of fasting IRI correlated closely in the preeclamptic group, suggesting an association between IRI and blood pressure in women

Downloaded from https://academic.oup.com/jcem/article/81/8/2908/2875655 by guest on 16 August 2022

TABLE 2. Serum concentrations of total cholesterol and its subfractions, triglyceride, and uric acid in women with and without a history of preeclampsia

	Women with prior preeclampsia or eclampsia (n = 22)	Control women (n = 22)	*P* value
Total cholesterol (mmol/L)	5.24 ± 0.14	4.98 ± 0.17	NS
HDL cholesterol (mmol/L)	1.85 ± 0.08	1.76 ± 0.08	NS
HDL_2 cholesterol (mmol/L)	0.66 ± 0.05	0.65 ± 0.05	NS
HDL_3 cholesterol (mmol/L)	1.19 ± 0.05	1.10 ± 0.05	NS
LDL cholesterol (mmol/L)	3.01 ± 0.12	2.87 ± 0.16	NS
Triglycerides (mmol/L)	0.86 ± 0.05	0.79 ± 0.06	NS
Uric acid (μmol/L)	275 ± 12	260 ± 11	NS

Values are the mean ± SE.

with a preeclamptic first pregnancy. Perhaps mild hyperinsulinemia, as seen in our study, may contribute to the increased risk of ischemic heart disease between 45–90 yr of life in these women (34).

Acknowledgments

We thank Ms. Marja-Leena Pekonen, Ms. Anna-Liisa Vuohijoki, Ms. Anja Mäki, and Ms. Tuula Soppela-Loponen for their technical assistance in performing these studies, and Dr. Per-Henrik Groop for the critical reading of the manuscript.

References

1. **Kaaja R, Tikkanen MJ, Viinikka L, Ylikorkala O.** 1995 Serum lipoproteins, insulin and urinary prostanoid metabolites in normal and hypertensive pregnant women. Obstet Gynecol. 85:353–356.
2. **Reaven BM.** 1988 Role of insulin resistance in human disease. Banting lecture 1988. Diabetes. 37:1595–1607.
3. **DeFronzo RA, Ferrannini E.** 1991 Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 14:173–194.
4. **Kaplan NM.** 1989 The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med. 149:1514–1520.
5. **National High Blood Pressure Education Program Working Group.** 1990 Report on high blood pressure in pregnancy. Am J Obstet Gynecol. 163:1689–1712.
6. **Town M-H, Gehm S, Hammer B, Ziegenhorn J.** 1985 A sensitive calorimetric method for the enzymatic determination of uric acid. J Clin Chem Clin Biochem. 23:591.
7. **Siedel J, Hägele EO, Ziegenhorn J, Wahlefeld A.** 1983 Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. Clin Chem. 29:1075–1080.
8. **Finley PR, Schifman RB, Williams J, Lichti DA.** 1978 Cholesterol in high-density lipoprotein: use of Mg/dextran sulfate in its enzymic measurement. Clin Chem. 24:931–933.
9. **Gidez LI, Miller GJ, Burstein M, Slagle S, Eder HA.** 1982 Separation and quantitation of subclasses of human plasma high density lipoproteins by a simple precipitation procedure. J Lipid Res. 23:1206–1223.
10. **Friedewald WT, Levy RI, Fredrickson DS.** 1972 Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 18:499–503.
11. **Wahlefeld AW.** 1974 Triglycerides. Determination after enzymatic hydrolysis. In: Bergmeyer HU, ed. Methods in enzymatic analysis, 2nd ed. New York: Academic Press; 1831–1835.
12. **Matthews JNS, Altman DG, Campbell MJ, Royston P.** 1990 Analysis of serial measurements in medical research. Br Med J. 300:230–235.
13. **Haffner SM, Mykkänen L, Valdez RA, et al.** 1994 Disproportionately increased proinsulin levels are associated with the insulin resistance syndrome. J Clin Endocrinol Metab. 79:1806–1810.
14. **Vuorinen-Markkola H, Yki-Järvinen H.** 1994 Hyperuricemia and insulin resistance. J Clin Endocrinol Metab. 78:24–29.
15. **Laakso M.** 1992 How good a marker is insulin level for insulin resistance. Am J Epidemiol. 137:959–965.
16. **Peiris AN, Mueller RA, Smith GA, Struve MF, Kissebah AH.** 1986 Splanchnic insulin metabolism in obesity. J Clin Invest. 78:1648–1657.
17. **Freedman DS, Srinivasan SR, Burke GL, et al.** 1987 Relation of body fat distribution to hyperinsulinemia in children and adolescents: the Bogalusa Heart Study. Am J Clin Nutr. 46:403–410.
18. **Modan M, Or J, Karasik A, et al.** 1991 Hyperinsulinemia, sex, and risk of atherosclerotic cardiovascular disease. Circulation. 84:1165–1175.
19. **Parker DR, Weiss ST, Troisi R, Cassano PA, Vokonas PS, Landsberg L.** 1993 Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations: the Normative Aging Study. Am J Clin Nutr. 58:129–136.
20. **Yki-Järvinen H.** 1984 Insulin sensitivity during menstrual cycle. J Clin Endocrinol Metab. 59:350–353.
21. **Toth EL, Suthijumroon A, Crockford PM, Ryan EA.** 1987 Insulin action does not change during menstrual cycle in normal women. J Clin Endocrinol Metab. 64:74–80.
22. **Bonora E, Zavarini I, Alpi O, et al.** 1987 Influence of the menstrual cycle on glucose tolerance and insulin secretion. Am J Obstet Gynecol. 157:140–141.
23. **Luukkainen T, Lähteenmäki P, Toivonen J.** 1990 Levonorgestrel-releasing intrauterine device. Ann Med. 22:85–90.
24. **Godsland IF, Walton C, Felton C, Proudler A, Patel A.** 1991 Insulin resistance, secretion, and metabolism in users of oral contraceptives. J Clin Endocrinol Metab. 74:64–70.
25. **Luotola H, Pyörälä T, Loikkanen M.** 1986 Effects of natural oestrogen/progestogen substitution therapy on carbohydrate metabolism in post-menopausal women. Maturitas. 8:245–253.
26. **De Cleyn K, Buytaert P, Coppens M.** 1989 Carbohydrate metabolism during hormonal substitution therapy. Maturitas. 11:235–242.
27. **Godsland IF, Gangar K, Walton C, et al.** 1993 Insulin resistance, secretion, and elimination in postmenopausal women receiving oral or transdermal hormone replacement therapy. Metabolism. 42:846–853.
28. **DeFronzo RA, Tobin JD, Reubin A.** 1979 Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 237:E214–E223.
29. **Adams EM, MacGillivray I.** 1961 Long-term effect of pre-eclampsia on blood pressure. Lancet. 2:1373–1375.
30. **Bryans CI.** 1966 The remote prognosis in toxemia of pregnancy. Clin Obstet Gynecol. 9:973–990.
31. **Chesley LC.** 1976 Remote prognosis after eclampsia. In: Lindheimer MD, Katz AI, Zuspan FP, eds. Hypertension in pregnancy. New York: Wiley and Sons; 31–40.
32. **Fisher KA, Luger A, Spargo BH, Lindheimer MD.** 1981 Hypertension in pregnancy: clinical-pathological correlations and remote prognosis. Medicine. 60:267–276.
33. **Sibai BM, El-Nazer A, Gonzales-Ruiz A.** 1986 Severe pre-eclampsia-eclampsia in young primigravid women: subsequent pregnancy outcome and remote prognosis. Am J Obstet Gynecol. 155:1011–1016.
34. **Jónsdottir LS, Arngrimsson R, Geirsson RT, et al.** 1995 Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. Acta Obstet Gynecol Scand. 74:772–776.

Downloaded from https://academic.oup.com/jcem/article/81/8/2908/2875655 by guest on 16 August 2022