

Short-term outcome of patients with preeclampsia

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Introduction: Preeclampsia constitutes a cause of increased mortality in mothers and fetuses. Screening for promoting factors is essential for adequate prevention in the event of any subsequent pregnancy, and for the adequate follow-up of concerned patients. The aim of the present study was to evaluate the short-term outcome of patients with preeclampsia and to identify possible new factors predisposing them to the disease.

Methods: One hundred fifty-five patients having experienced preeclampsia between 2005 and 2010 from the Gynecology and Obstetrics Department of the Foch Hospital (Suresnes, France) were included in the study. All patients had undergone close clinical and standard biological follow-up immediately postpartum and then 3 months later with a reference practitioner. In severe cases, further investigation was carried out by full etiological examination with an assessment of both autoimmune and thrombophilic status.

Results: Obesity and gestational diabetes were observed to be major risk factors for preeclampsia, which were found in 46% and 15% of the cases, respectively. The etiological assessment showed abnormalities in 11% of the patients. Impaired thrombophilia was found in 3% of the patients, impaired autoimmune status in 4%, a combination of both abnormalities in only 1% of the patients, and detection of renal abnormalities in 3% of the patients were observed. In the immediate postpartum period, 66% of patients had maintained elevated blood pressure levels, and 66% had proteinuria > 0.3 g/24 hours. At the 3-month postpartum assessment, persisting arterial hypertension was found in 16% of the patients, requiring continuation of antihypertensive therapy, and 22% of the patients had proteinuria over the accepted threshold (0.15 g/24 hours).

Conclusion: Patients with preeclampsia have increased cardiovascular risk, necessitating lifestyle measures and long-term follow-up. Etiological assessment must be carried out, systematically aiming at the detection of promoting underlying diseases and adaptation of the management of subsequent pregnancies.

Keywords: preeclampsia, postpartum, gestational hypertensive disorders

Introduction

Gestational hypertension is a frequent disorder that affects 6% to 15% of pregnant women.¹ In 2% to 5% of these women, proteinuria is associated, resulting in a specific secondary hypertension, referred to as preeclampsia.² Such a complication occurs typically during the third trimester of pregnancy and usually resolves postpartum, but clinical and biological abnormalities may persist. Several risk factors of preeclampsia have been identified such as primiparity and a personal history of hypertension,³ while others such as thrombophilia, autoimmunity, or renal disease remain debated especially due to the fact that the pathophysiological mechanisms of preeclampsia remain incompletely elucidated. The aim

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of this study was to examine the outcome of preeclamptic patients in the immediate and short-term postpartum period, and to identify its predisposing factors.

Methods

This prospective study analyzed data from 155 patients treated in our department (Foch Hospital, Suresnes, France) from January 2005 through December 2010, having presented with preeclampsia during their pregnancy.

Preeclampsia was defined as the combination of arterial blood pressure (BP) ≥ 140 mmHg for systolic BP (SBP) and/or ≥ 90 mmHg for diastolic BP (DBP), as well as proteinuria ≥ 0.30 g/24 hours. Severe preeclampsia was defined by the presence of at least one of the following criteria: severe hypertension (SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg); renal impairment (oliguria < 500 mL/24 hours or creatinine > 135 mmol/L, or proteinuria ≥ 5 g/24 hours); acute pulmonary edema, persistent epigastric pain, or hemolysis-elevated-liver-enzymes-and-platelet (HELLP) syndrome; eclampsia or refractory neurological disorders (visual, auditive, polykinetic vivid deep tendon reflex, cephalalgias); thrombocytopenia; retroplacental hematoma; or impact on the fetus.

Collected data included the following: personal medical and obstetrical history, actual signs of gravity, biological abnormalities, need for antihypertensive therapy, and obstetrical outcome. The whole set of data was collected from the computerized obstetrical and nephrologic patients' files. In case of missing data, information was requested from both the patient and the attending doctor.

Immediately after delivery (< 5 days postpartum), each patient had undergone clinical examination (BP assessment, screening for symptoms of hypertension) and biological follow-up (proteinuria, complete blood cell count, hepatic enzymes, creatinine, uricemia) in order to assess the improvement of the clinical and biological state. For those women requiring continuation of antihypertensive therapy after hospital discharge, a recommendation letter was addressed to the attending practitioner regarding the need for follow-up and potentially for treatment management.

Nephrologic evaluation was systematically scheduled 3 months postdelivery, based on the clinical examination (weight, BP) and biological assessment including monitoring of the renal function and etiological work-up: blood ionogram and blood urea, creatinine, protein, albumin and calcium; 24-hour proteinuria, urine cytobacteriological examination, complete blood cell count, platelets, activated partial thromboplastin time, prothrombin index, fibrinogen,

antinuclear factors, and native antideoxyribonucleic acid antibodies. In case of complication such as the occurrence of eclampsia, HELLP syndrome, severe intrauterine growth restriction, intrauterine fetal death (IUFD), or retroplacental hematoma, complete thrombophilia assessment was carried out, which included: determination of C and S proteins; factors 7 and 8; search for activated protein C resistance; for factors 2 and 5 Leyden mutation; antithrombin 3 deficiency; hyperhomocysteinemia, methylenetetrahydrofolate reductase gene mutation, and determination of anticardiolipin and antiphospholipid antibodies. This evaluation was also aimed at screening for potential risk factors so as to adapt management in case of subsequent pregnancy and to provide advice regarding long-term cardiovascular risk.

Results

Study population

The clinical characteristics of the study population and their preeclampsia risk factors are shown in Table 1. The 155 patients who experienced preeclampsia during their pregnancy had an average age of 31.9 years (range, 18–51 years). Most of the patients (63.2%) were nullipara; among multipara women, 35% had already experienced preeclampsia; preventive aspirin-like therapy had been prescribed in 14% of this subset. Five had experienced very severe and complicated preeclampsia with IUFD. Personal and familial history of hypertension was found in 18.1% and 35.5% of patients, respectively. Overweight (body mass index > 25 kg/m²) and/or obesity were affecting nearly half of the sample, and gestational diabetes was associated in 22 patients (assessed between 24 and 26 weeks gestation), preexisting in only three.

Table 1 Clinical characteristics of the population and preeclampsia risk factors (n = 155)

Mean age (years)	31.9 (18–51)	
	Number	Percentage
Primipara	98	63
Multipara	57	37
History of preeclampsia	20	35
Severe preeclampsia with IUFD	5	9
Aspirin intake	8	14
Preeclampsia risk factors		
Personal history of hypertension	28	18
Familial history of hypertension	55	35
Obesity/overweight	72	46
Preexisting diabetes	3	2
Gestational diabetes	22	14
Preexisting nephropathy	2	1
History of preeclampsia	20	35

Abbreviation: IUFD, intrauterine fetal death.

Preeclampsia description and pregnancy outcome

Preeclampsia as observed in this study is described in Table 2. In most cases, the first clinical sign was gestational hypertension (SBP \geq 140 mmHg and/or DBP \geq 90 mmHg), necessitating close monitoring with or without antihypertensive treatment. The occurrence of significant values of proteinuria (\geq 0.3 g/24 hours) allowed for the confirmation of a preeclampsia diagnosis. The onset of preeclampsia was observed at 15 weeks of amenorrhea (WA) as the earlier time, and 36 WA as the later time.

Severe hypertension was present in 43.9% of the patients, while excessive proteinuria was observed in 15.5%. Lower limb edema was very frequent with an incidence of 64.5%, and hypertension-related functional signs were present in 27.7% of the patients. Biochemistry showed frequent hyperuricemia (48.4%), and more or less important, cytolysis was present in 22.5%. Preeclampsia was observed to be complicated in 13.5% of the patients by intrauterine growth restriction, in 14.8% by a HELLP syndrome, in 4.5% by IUFD, and in 1.3% by a retroplacental hematoma. Overall, 43.2% of the patients were requiring prescription of an antihypertensive therapy during their pregnancy.

Pregnancy outcome is shown in Table 3. The average time of delivery was 37.3 WA, the earlier one being at 24 WA with neonatal death. Eighty nine patients (57.4%) spontaneously initiated labor, including those who developed preeclampsia during the postpartum period, and 66 (42.6%) necessitated maturation or labor induction due to preeclampsia. In 49% of the patients, caesarean section was to be carried out either directly (32.1%), or after failure of labor induction, or due to

Table 2 Characteristics of preeclampsia

n = 155	Number	Percentage
Severe preeclampsia (SBP \geq 160 and/or DBP \geq 100 mmHg)	67	43
Proteinuria \geq 5 g/24 hours	24	15
Lower limb edema	100	66
Hypertension functional signs	43	28
Impaired biochemistry		
Hyperuricemia	75	48
Incomplete HELLP syndrome: cytolysis	35	23
Complications		
Intrauterine growth restriction	21	14
HELLP syndrome	23	15
Intrauterine fetal death	7	5
Retroplacental hematoma	2	1

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HELLP, hemolysis-elevated-liver-enzymes-and-platelet; n, number.

Table 3 Pregnancy outcome (n = 155)

Mean term of delivery	37.3 weeks of amenorrhea	
	Number	Percentage
Induction of labor	66	43
Vaginal delivery	79	51
Spontaneous	38	25
After induction	41	26
Caesarean delivery	76	49
Directly	51	32
After failed labor induction or AFD	25	16

Abbreviations: n, number; AFD, acute fetal distress.

acute fetal distress (16.1%). In seven patients, the severity of the condition resulted in IUFD.

Follow-up: clinical, biochemistry and etiological assessments

During the postdelivery hospital stay (<5 days), clinical and biological follow-up was carried out; the results are shown in Table 4. High BP was observed in a high proportion of the patients (65.8%), necessitating specific treatment in 63.2%, and 66.5% had significantly elevated proteinuria. Persistent hyperuricemia and/or cytolysis were present in 28.4%. Delayed HELLP syndrome occurred in three patients.

A systematic nephrologic visit at month 3 postpartum was scheduled; 64.5% of the patients underwent this evaluation. For those women lacking the nephrologic evaluation (except 23 for whom we did not manage to obtain such information), data on BP progression, need for therapy, and proteinuria status were collected by direct questioning of the patient or her physician. High BP was persistent in 16.1% of the patients, requiring continuation of antihypertensive therapy. Excessive proteinuria was persistent in 21.9% (Table 5).

The etiological assessment showed abnormalities in about 11% of the patients, of which the most frequent was an impairment of the thrombophilic and autoimmune status (Table 6). Renal disease was suspected or evidenced more rarely.

Table 4 Progression of the clinical and biological parameters in immediate postpartum

n = 155	Number	Percentage
Persistent high blood pressure	102	66
Need for antihypertensive therapy	98	63
Proteinuria \geq 0.3 g/24 hours	103	66
Proteinuria < 0.3 g/24 hours	26	17
Cytolysis/hyperuricemia	44	28
Delayed HELLP syndrome	3	2
Normal biochemistry	111	72

Abbreviations: n, number; HELLP, hemolysis-elevated-liver-enzymes-and-platelet.

Table 5 Blood pressure and proteinuria evolution

n = 155	Immediately postpartum		At 3 months	
	Number	Percentage	Number	Percentage
Persistent high blood pressure and need for therapy	102	65	25	16
Persistent significant proteinuria	103	66	34	22
Blood pressure normalization	53	34	107	69
Lost to follow-up	0	0	23	15

Abbreviation: n, number.

One case of Berger disease was observed in a patient with late combined proteinuria and macroscopic hematuria, although renal biopsy did not reveal typical lesions. In another patient, renal biopsy was performed due to combined high proteinuria (3.35 g/24 hours) persisting after 3 months, and renal failure resulting in a histological diagnosis of renal disease with mesangial deposition of immunoglobulin A. Independent of preeclampsia, one case of malformative uropathy with impaired renal function and one case of a benign 10 cm cyst were identified, allowing for adequate management and follow-up.

Discussion

The preeclampsia risk factors identified in our series are displayed in Table 1. As in other studies, primiparity was shown to be a major risk factor; about two-thirds of our population developed preeclampsia during their first pregnancy. A systematic review of controlled studies carried out in 2005 confirms such observation with an adjusted

risk ratio (RR) of 3.1 (1.55–6.17; 95% confidence interval [CI]),³ and also reports an incidence of preeclampsia that was significantly higher in overweight patients, with a RR of 2.47 (1.66–3.67; 95% CI) (six studies; n = 64,789). Our results are in accordance with the findings from this review, since among the major findings of our study, obesity appears to be a significant promoting factor, with almost half of the study sample of preeclamptic patients suffering from overweight or obesity. In a review by Duckitt and Harrington,³ diabetes was also clearly observed to promote the onset of preeclampsia, with a RR of 3.56 (2.54–4.99; 95% CI) (three studies; n = 56,968). In our study, 22% of patients developed gestational diabetes, results that were consistent with those of Brown et al,⁴ who reported a significant relationship between preeclampsia and diabetes ($P = 0.03$). Interestingly, in the study by Forest et al⁵ aimed to determine a potential relationship between the onset of gestational hypertension and the presence of metabolic syndrome, with obesity and diabetes being the two main entities of this syndrome. It was found that women with metabolic syndrome were shown to have a three- to fivefold increased risk for gestational hypertension.

The elevation of BP in preeclampsia is generated by many mechanisms that are not all elucidated. Sibai et al⁶ propose a potential scenario that involves immunologic mechanisms that cause placentation deficiency and generalized endothelial dysfunction, combining vasoconstriction, hemostasis activation, and imbalanced prostaglandins/thromboxane, favoring the latter. Placental ischemia occurs with the release of substances that cause endothelial inflammatory reaction, thus resulting in increased BP. Consequently, pregnancy termination should induce the regression of such phenomena and preeclampsia symptoms. In the present study, 65.8% of the patients had still elevated BP in the postdelivery days. In addition, 16.13% of patients had persistently high BP 3 months later, necessitating continuation of antihypertensive therapy. Several studies have suggested that pregnancy termination is not always synonymous with BP normalization. Dekker et al⁷ observed high BP 10 weeks postdelivery in 38% of their sample, with severe early preeclampsia (n = 101). Our study has focused on the short-term

Table 6 Abnormalities observed at the etiological assessment

Abnormality	Cases
Renal anomalies	4 <ul style="list-style-type: none"> • 1 urinary reflux • 1 glomerulonephritis with deposition of IgA • 1 Berger disease • 1 renal 10 cm cyst
Impaired thrombophilia	5 <ul style="list-style-type: none"> • 3 protein S deficiency • 1 significant increase of factor 8 • 1 heterozygote MTHFR mutation + heterozygote factor 5 Leyden mutation + hyperhomocysteinemia
Impaired autoimmune status	6 <ul style="list-style-type: none"> • 4 antinuclear antibodies + (including 1 with anti-SSB + antibodies) • 2 antiphospholipin antibodies + isolated
Impaired thrombophilia + impaired autoimmune status	2 <ul style="list-style-type: none"> • 1 heterozygote MTHFR mutation + antiphospholipin antibodies • 1 factor 5 Leyden mutation + antinuclear + native anti-DNA antibodies

Abbreviations: MTHFR, methylenetetrahydrofolate reductase; IgA, immunoglobulin A; DNA, deoxyribonucleic acid.

BP outcome, but others examined long-term complications of preeclampsia and hypertension, which appear to be frequent. In a large meta-analysis of 113 studies, Williams et al⁸ have evidenced an increase in this risk, with a RR of 3.70 (2.70–5.05; 95% CI). For the longer term, Sibai et al⁶ carried out a 25-year follow-up of patients with a history of preeclampsia versus a control group, and assessed the risk of developing chronic hypertension. The overall incidence of chronic hypertension was significantly higher in patients with preeclampsia (14.8% versus 5.6%; $P < 0.0001$), which clearly indicates an increase of this risk with time.

A systematic thrombophilia assessment was undertaken in patients with severe preeclampsia. Impaired thrombophilic status was found in about 5% of the study patients. Dekker et al⁷ were the first to describe an increased prevalence of thrombophilic disorders in women with early and severe preeclampsia. In their study, 53 of 101 women had presented with HELLP syndrome, 24.7% of the patients had protein S deficiency, 16% activated protein C resistance (factor V Leyden mutation) and 17.7% had hyperhomocysteinemia. The incidence of these abnormalities was significantly increased compared with the general population. Similarly, Kupferminc et al⁹ compared the prevalence of coagulation abnormalities between women with complicated preeclampsia during pregnancy and a control group of women with normal pregnancy. Impaired thrombophilic status was 8.2 times more frequent in preeclamptic women (4.4–15.3; 95% CI).

In this study, a systematic nephrology visit at month 3 postpartum was scheduled, but data from 14.8% of the population were missed (lost at follow-up), which may constitute a limitation in the study. Despite this relatively high percentage, our results are consistent with those published previously. Decreased renal plasma flow, decreased glomerular filtration rate, and the presence of proteinuria are the main renal manifestation of preeclampsia; however, the exact mechanisms involved and the renal consequences remain incompletely understood. Also, the hypothesis of a renal predisposition to such pathology has often been suggested, but this remains unclear. Fisher et al¹⁰ found histological lesions in 9.2% of primipara patients and up to 37% in multipara women with reoccurring preeclampsia (in addition to classical glomerulosclerosis lesions), suggesting that an underlying renal disease was present while gestational disease developed. More recently, Suzuki et al¹¹ have carried out diagnostic renal biopsies in 127 postmenopausal women with chronic renal failure, and compared the histological lesions observed in 32 women with a history of preeclampsia and those of 95 controls. Their results illustrate a lesion

distribution that was significantly different, with 12 patients exhibiting focal segmental glomerulosclerosis in patients with a significant history of preeclampsia versus those with no lesions in controls. As such, the authors suggested that this disease is likely to induce renal sequels, which are specifically responsible for renal failure in the future.¹¹

In our study, 21.94% of the patients presented with proteinuria at the third month postpartum, which seems to indicate a slow restoration of normal renal function with persistent abnormalities, as suggested by others.¹² The renal abnormalities observed in our study may not be directly incriminated in the development of the gestational disease, but the potential role of a glomerular disorder in precipitating the onset of preeclampsia may not be ruled out. Reports on this topic remain insufficient, especially due to the invasive pattern of renal biopsy and its restricted indications.

The present study showed that no cardiovascular event had occurred during the 3-month follow-up period, which elsewhere may constitute a short period of time for the occurrence of cardiovascular events; therefore, this is a limitation of the present study. Many authors who studied the long-term outcome in preeclamptic women have observed an increased cardiovascular risk in this population. Wilson et al¹³ have shown an adjusted RR of 3.59 (1.01–12.4; 95% CI) regarding the risk of stroke-related death. Other authors have reported similar results with a twofold increased risk of ischemic heart disease or deep venous thrombosis in preeclamptic women.^{14–16} Such results were confirmed in 2008 by McDonald et al¹⁵ who carried out a meta-analysis on long-term morbidity in preeclampsia. Furthermore, this risk appears to be correlated to an early time of onset and the severity of preeclampsia during pregnancy; the RR of coronary disease increases from 2.99 (2.51–3.58; 95% CI) in moderate preeclampsia to 5.39 (3.96–7.27; 95% CI) in severe preeclampsia. Two types of hypotheses currently attempt to explain the relationship between preeclampsia and vascular disease: transient but severe endothelial dysfunction responsible for vascular lesions promoting arteriosclerosis,¹⁷ or conversely, the existence of predispositions likely to express such disorders. Most probably, a combination of both is present in most preeclamptic women. More recently, Radman et al¹⁸ also reported that preeclampsia, low birth-weight delivery and high parity of the mother as independent risk factors for coronary artery disease in the future.

Conclusion

Preeclampsia is a gestational complication of which the predisposing factors, mechanisms, and obstetrical

consequences have become better known. It is commonly acknowledged today that pregnancy termination induces resolution of this disease, but surveillance of the patients must not stop after delivery. In fact, etiological assessment should be systematically carried out to search for underlying diseases and to adapt the management of any subsequent pregnancy. Preeclamptic patients also seem to be at greater cardiovascular risk, and long-term follow-up appears to be crucial.

Disclosure

The authors report no conflicts of interest in this work.

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