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NEPHROLOGY FORUM

Hypertension in pregnancy: A case discussion

Principal discussant: C. W. G. REDMAN

John Radcliffe Hospital Maternity Department, and University of Oxford, Oxford, U.K.

Case presentation

A 25-year-old white woman was transferred to the John Radcliffe Hospital, Oxford, at 23 weeks in her first pregnancy because of a blood pressure of 200/130 mm Hg and intermittent proteinuria. At the age of 17 years, she developed left hemiparesis and a mild concussion after a fall. A right-sided carotid arteriogram was normal. Her blood pressure was 120–160/70–96 mm Hg. The neurologic abnormalities persisted. After a spontaneous "blackout," more investigations, including an air encephalogram, also were normal. Because marked systolic hypertension (220/70 mm Hg) with tachycardia was detected when she was 19 years old, she was treated with propranolol. Investigations included two CT body scans, intravenous pyelography, urinary VMA excretion, and thyroid function tests, all of which were normal. At the age of 24 years she had right-sided pyelonephritis. The blood pressure was then 220–260/110–180 mm Hg; methyldopa, propranolol, and bendrofluazide were prescribed. At the age of 25 she again lost consciousness spontaneously.

Shortly afterwards she conceived while taking propranolol and bendrofluazide. At 8 weeks into gestation, her blood pressure was 160/100 mm Hg, settling to 140/90 at 15 weeks. At that time she had no proteinuria. By the time of her transfer (at 23 weeks), methyldopa, debrisoquine, and chlorpromazine had been added to the regimen to control the increasing blood pressure. Physical examination was normal apart from wasting and reduced function in the left arm. The kidneys were not palpable and there were no renal artery bruits. Peripheral pulses were present and synchronous. The retinal arterioles were not narrowed and no hemorrhages or exudates were present. Fetal size and heart rate pattern also were normal. The plasma creatinine was 0.5 mg/dl; uric acid, 4.1 mg/dl; and 24-hour urinary protein excretion, 0.84 g. Platelet count was 293,000/mm^3; the ratio of Factor VIII-related antigen to clotting activity was 1.27. Liver function tests were normal.

Her treatment was changed to methyldopa, labetalol, and hydralazine, for which oral diazoxide was later substituted. Nevertheless her blood pressure continued to be unstable, repeatedly reaching 200/130 mm Hg but with a lower baseline of approximately 160/110 mm Hg. The peaks in arterial pressure were associated with prostrating paroxysms of severe headaches, vomiting, and tachycardia. Plasma catecholamine concentrations as well as urinary excretion of 4-hydroxy 3-methoxy mandelic acid (HMMA) were normal. She continued to have proteinuria (up to 2.3 g/24 hours), but renal function remained normal; plasma creatinine was always less than 0.7 mg/dl and uric acid less than 5.0 mg/dl. Repeated midstream samples of urine were unremarkable except for asymptomatic bacilluria that was treated appropriately. The platelet count was always greater than 250,000/mm^3, but the Factor VIII ratio rose slowly to 2.27 by the 35th week of pregnancy.

At 35 weeks, labor was induced. The patient delivered vaginally a healthy son weighing 2340 g (10th–25th percentile) who did not need special care. After delivery the patient's symptoms and the instability of her blood pressure remitted. On discharge, propranolol, 160 mg four times a day, was prescribed. Six weeks later the blood pressure was 148/98 mm Hg, renal function was normal, and no proteinuria was present. She was feeling extremely well.

She remained under the care of her local physician until 3 years later, when she presented at 16 weeks into her second pregnancy. She was taking atenolol and the blood pressure was 160/100 mm Hg. The course of the second pregnancy was characterized, as was the first, by paroxysms of prostrating headaches, vomiting, extreme hypertension, and tachycardia. A CT scan of the skull was normal. By the end of her pregnancy she was taking atenolol, methyldopa, slow-release nifedipine, and an antiemetic. Her renal function remained normal. Proteinuria was recorded sporadically but never reached more than 0.4 g/24 hours. After a normal delivery at 35 weeks (a healthy daughter, 2160 g, 10th–25th percentile for gestational age), her symptoms again remitted; by 6 weeks postpartum the blood pressure was 158/84 mm Hg while she was taking atenolol, and she felt entirely well. Renal function was normal and proteinuria had disappeared.

Discussion

DR. CHRISTOPHER W. G. REDMAN (*University Lecturer and Consultant in Obstetric Medicine, University of Oxford, Oxford, U.K.*): In her first pregnancy the patient was transferred at 23 weeks gestation with the provisional diagnosis of severe pre-eclampsia superimposed on pre-existing hypertension. It is unusual but not rare for cases of pre-eclampsia to present between 20 and 28 weeks; indeed rare cases have been reported to occur even before 20 weeks of pregnancy [1]. Presentation before 28 weeks creates a particular problem because delivery under these circumstances may be incompatible with fetal survival.

Pre-eclampsia usually progresses through three distinct stages: hypertension alone, proteinuric hypertension without symptoms, and proteinuric hypertension with symptoms.

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Finally, eclampsia ensues. Characteristically, the speed of the progression accelerates so that the symptomatic third stage may last only a few hours and, at most, a few days. A woman with symptomatic pre-eclampsia therefore must be delivered without delay regardless of gestational maturity. At presentation this patient appeared to have proteinuric pre-eclampsia without symptoms (stage 2), which shortly afterwards was associated with severe headaches and vomiting—the typical pre-eclamptic symptoms. Thus an argument could have been made for urgent delivery. But several of her features were so atypical that we believed the diagnosis of pre-eclampsia could be excluded with reasonable certainty and that the pregnancy could be continued safely. Today I will discuss this patient in some detail, simultaneously examining some of the major characteristics of the pre-eclamptic syndrome.

The pre-eclamptic syndrome: Primary pathology

Because pre-eclampsia has no known cause, there is no precise diagnostic test—the condition can be identified only as a syndrome. The primary pathology, which is within the uterus, results from the presence of trophoblast but not necessarily a fetus because pre-eclampsia can occur with hydatidiform mole [2]. The fundamental problem is probably an insufficient blood supply to the placenta. In the first half of pregnancy, the spiral arteries of the placental bed are infiltrated by trophoblast; this process causes these arteries to dilate [3]. Then the uteroplacental blood flow can increase normally in the second half of pregnancy. In pre-eclampsia this process fails [4]. The ensuing restriction in uteroplacental perfusion is exacerbated by the development of obstructive lesions of the spiral arteries; these lesions, termed "acute atherosis," are composed of lipid-filled macrophages and thrombi [5]. Uteroplacental blood flow is reduced [6], and the placenta shows histologic features of ischemia [7] or frank infarction [8]. Placental ischemia is thus a major feature of pre-eclampsia.

The maternal features of pre-eclampsia are thought to be secondary to the underlying placental ischemia, although definite proof is still lacking. However, there is circumstantial evidence in that several animal models of pre-eclampsia have been produced by inducing placental ischemia [9–11]. The maternal manifestations of pre-eclampsia can involve the arterial tree, the clotting system, the kidney, the liver, and the nervous system, but the specific pattern of maternal abnormalities varies greatly from one individual to another.

Secondary involvement of the arterial tree

Systemic hypertension in pre-eclampsia primarily results from an increase in peripheral resistance [12]; cardiac output typically remains unchanged [13]. The hypertension is preceded by increased reactivity of the maternal circulation to the infusion of angiotensin II [14]; this finding is thought to be mediated by changes in prostanoid metabolism [15]. Typically, a pre-eclamptic woman has an unstable arterial pressure despite bed rest [16] with a loss, and ultimately a reversal [17], of the normal, nocturnal fall of the pressure during sleep.

The differential diagnosis of hypertension in pregnancy

Hypertension in the second half of pregnancy is a common and difficult problem. Frequently recordings of the woman's arterial pressure before she became pregnant are not available. Pregnancy normally induces a fall in pressure that occurs mainly during the second half of the first trimester [18] and in some cases is large enough to obscure pre-existing hypertension. An extreme example has been reported of a woman whose pre-pregnancy blood pressure readings were 224–280/140–180 mm Hg; during pregnancy the pressure fell without treatment (not available at the time) to 110–130/60–80 mm Hg [19]. The blood pressure normally rises to pre-pregnant levels at the end of the third trimester; women whose pressure falls in mid-trimester are those whose pressure rises at the end of pregnancy [20]. Hence a rise in the arterial pressure in the third trimester from earlier, normal levels does not necessarily indicate pre-eclampsia. The significance of the change can be assessed only retrospectively by later, postpartum investigation.

Diagnosing pre-eclampsia is easier when a well-documented series of blood pressure readings before pregnancy is available. If the pregnancy progresses normally, the blood pressure may run at a higher baseline in chronically hypertensive women, but other features of pre-eclamptic hypertension are not present, including baseline blood pressure instability, altered circadian rhythm, and increased pressor sensitivity to exogenous angiotensin II [21].

Hypertension with paroxysmal features, as exemplified by the present patient, suggests pheochromocytoma. The presentation of pheochromocytoma in pregnancy can simulate pre-eclampsia, with similar symptoms, unstable hypertension, and proteinuria. The symptoms can remit between pregnancies [22]. Maternal mortality from pheochromocytoma is high [23], particularly postpartum. For this reason, all women with severe pre-eclampsia, regardless of symptoms, should be screened for the presence of pheochromocytoma. The usual tests of urinary catecholamines or their metabolites can yield false-negative results; a maternal death from pheochromocytoma was recorded with three normal results for urinary VMA excretion [24]. If one suspects pheochromocytoma, plasma catecholamine levels should be measured. In the patient we are discussing today, the possibility of a pheochromocytoma already had been investigated before pregnancy, and two attempts using CT scans to localize a tumor had been negative. Additional measurements of plasma and urinary catecholamines were normal during the pregnancy.

Unstable blood pressures and severe headaches occur during the third trimester and in labor in women with high spinal cord transections (autonomic hyperreflexia) [25]. The paroxysms frequently are triggered by distension of the hollow viscera [26] and depend on intact autonomic spinal reflexes released from hypothalamic control. The problem may be induced for the first time or exacerbated in paraplegic women during pregnancy and then resolve after delivery [27]. Today's patient did not have a spinal lesion but had sustained a head injury and hemiparesis. It is possible, but not likely, that higher control of spinal reflexes had become disturbed at the same time, leading to the vasomotor instability that was a central feature of her pregnant state.

Other causes of hypertension are unlikely to explain the paroxysms experienced by this woman. There was no evidence of active glomerulonephritis, and a major degree of interstitial nephritis had been excluded by the normal pyelogram and renal function. Renal arteriograms had not been obtained (at the patient's request) and so renovascular hypertension could not

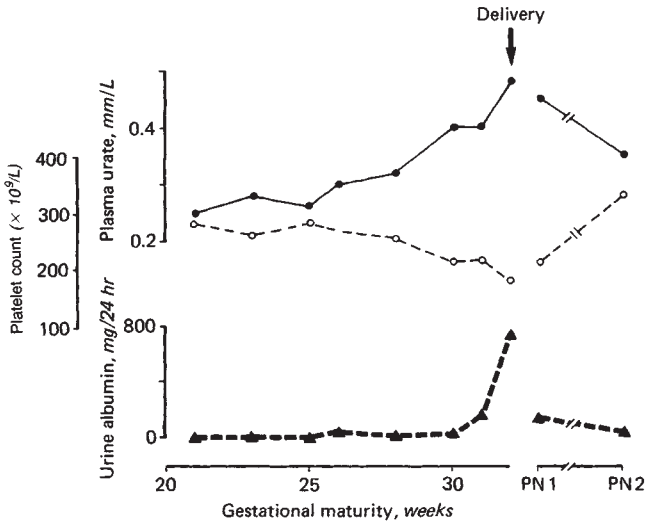

Fig. 1. *Serial measurements of maternal plasma urate (●—●), blood platelet count (○---○), and 24-hr urinary albumin excretion (▲---▲) from a patient who developed proteinuric pre-eclampsia requiring elective delivery at 32 weeks of pregnancy.* PN1 and PN2 refer to measurements 1 and 6 weeks after delivery. Urinary albumin was measured by a double antibody radioimmunoassay with a sensitivity of 125 μg/liter. The change in urinary albumin excretion was sudden and was preceded by a rising plasma urate and falling platelet count. 0.2 and 0.4 mM of urate are equivalent to 3.4 and 6.8 mg/dl respectively. (Reproduced from Ref. 30.)

be discounted. The histories of the few published cases of renal artery stenosis in pregnancy have been unlike that of the patient under discussion and, in particular, without mention of paroxysmal hypertension or symptoms.

Secondary involvement of the renal system

Renal involvement in pre-eclampsia, one of the syndrome's more consistent features, has long been recognized. The presence of proteinuria reflects advanced disease and is associated with a poorer prognosis [28]. If persistent proteinuria in excess of 0.5 g/day is present, our experience indicates that conservative management can prolong the pregnancy by 12 days on average (unpublished data). The relentless progression of pre-eclampsia then produces problems that make delivery inevitable. These problems include uncontrollable hypertension, deteriorating renal function, clotting or hepatic abnormalities, nausea, vomiting, headaches (phase 3 of the disease), or impending fetal death. There is considerable variability in the time course: in some, the proteinuric phase lasts 2 or 3 days only; in others, it may extend to 3 weeks or more. Hence, in clinical practice, the concept of proteinuric pre-eclampsia is useful. After about 34 weeks of pregnancy, proteinuria identifies a situation that is best resolved by elective delivery without delay. At earlier stages of pregnancy, delivery can be delayed despite the presence of proteinuria; the expected gain in fetal maturity is small but not necessarily trivial.

Cases of eclampsia, without proteinuria, have been reported [29], hence neurologic complications can be severe in the absence of severe renal involvement. This paradox illustrates a general principle of diagnosis of syndromes such as pre-eclampsia: the absence of a single sign never excludes with certainty the problem in question.

Table 1. Protein clearance in 16 patients with pre-eclampsia[a]

	Molecular weight (*daltons*)	Protein clearance (*% of transferrin clearance*)
Transferrin	90,000	[100%]
Albumin	69,000	99.4 ± 11.7
IgG	160,000	23.7 ± 3.7
B_1A/C globulin	250,000	4.6 ± 2.0
Pseudocholinesterase	300,000	4.8 ± 2.2
Alpha-2-macroglobulin	820,000	1.0 ± 0.3
IgM	1,000,000	0.8 ± 0.3

[a] The 16 patients were selected because of a rise in arterial pressure to 140/90 mm Hg or more with the onset of proteinuria (0.8–9.6 g/24 hr). The slope of the regression line of urinary clearance against molecular weight was used as an index of selectivity which, for these patients, was intermediate in value. (Adapted from Ref. 31.)

The proteinuria in pre-eclampsia is not preceded by a phase of microalbuminuria [30] (Fig. 1). The proteinuria is moderately selective [31] (Table 1), increases until the time of delivery, and occasionally exceeds 10 g/24 hours. Indeed, pre-eclampsia is the commonest cause of heavy proteinuria in pregnancy [32]. A nephrotic syndrome can ensue in which generalized edema, hypoproteinemia [33], reduced plasma oncotic pressure [34], and hypovolemia [35] can be present. Serous effusions, particularly ascites, occur. Respiratory difficulties may arise from laryngeal edema [36] or pulmonary edema [37]; cerebral edema can occur [38] and is a possible cause of at least some cases of eclampsia.

Renal involvement in pre-eclampsia has other well-documented features, including characteristic glomerular histology and changes in function. We do not use renal biopsy in the differential diagnosis of pre-eclampsia, however atypical or difficult the presentation. Biopsy is reserved for patients with persistent, significant proteinuria and renal impairment long after delivery. It has been claimed [39] and denied [40] that the glomerular lesions are pathognomonic. The former view incorporates a logical paradox because it implies that pre-eclampsia is a primary renal disease, which is improbable, given that pre-eclampsia is not merely pregnancy specific but, in most cases, parity specific. Normal renal histology has been documented in some patients with eclampsia [41], so this finding does not exclude the diagnosis. The variable degree to which the kidneys are involved (measured by proteinuria, changes in function, or renal histology) is to be expected if these are secondary manifestations of a primary uteroplacental problem.

The glomerular endothelial cells are found to be swollen, a histologic abnormality that has been termed "glomerular endotheliosis" [39]. Opinions differ as to whether the endothelial and mesangial cells proliferate [42–44] or the basement membrane is affected [44, 45]. Subendothelial electron-dense deposits typically are found [42], but the epithelial foot processes remain intact. Similar changes are found in the renal biopsies of women who have suffered placental separation—which may be complicated by shock and disseminated intravascular coagulation (DIC) [46]. This observation has two possible interpretations. Either the lesion is not specific for pre-eclampsia (but to antenatal DIC), or the placental abruption

Table 2. Renal function in pre-eclampsia[a]

	Serum urea nitrogen (*mg/dl*)	Serum uric acid (*mg/dl*)
Normal women (third trimester)	8.95 ± 2.36 (30)	3.57 ± 0.69 (30)
Chronic hypertension	10.75 ± 4.32 (10)	3.71 ± 1.07 (12)
Pre-eclampsia, severity 1+	9.22 ± 2.50 (9)	5.53 ± 1.74 (12)
Pre-eclampsia, severity 2+	10.82 ± 3.37 (11)	6.33 ± 1.37 (12)
Pre-eclampsia, severity 3+	13.06 ± 4.72 (9)	7.76 ± 1.54 (9)

[a] The diagnoses in this study were made by renal biopsy carried out during pregnancy. The grading of the severity of pre-eclampsia is histologic. The serum measures are given as mean ± one standard deviation, with the numbers of observations in parentheses. From these data it was concluded that the best clinical correlate of the glomerular pathology was provided by serum uric acid measurements. (Adapted from Ref. 45.)

Table 3. Evolution of severe pre-eclampsia in 14 patients followed serially[a]

Mean age (*years*)	26.6 ± 4.3
Primipara	9/14
Gestational age (weeks ± S.D.) at:	
First assessment	17.3 ± 2.8
Time of rising plasma uric acid	25.2 ± 3.8
Time of rising plasma urea	28.3 ± 3.1
Onset of proteinuria (11 patients only)	28.6 ± 3.1
Delivery	31.8 ± 2.8
Mean birthweight (*kg*)	1.3 ± 0.4
Surviving infants	10/14

[a] The 14 patients were studied serially through pregnancy, from an average gestational age of 17 weeks until early delivery. Rising plasma uric acid and urea levels were considered present if measurements were consistently 2.0 mg/dl and 5.0 mg/dl, respectively, above baseline levels. The onset of hyperuricemia before proteinuria is demonstrated. (Adapted from Ref. 51.)

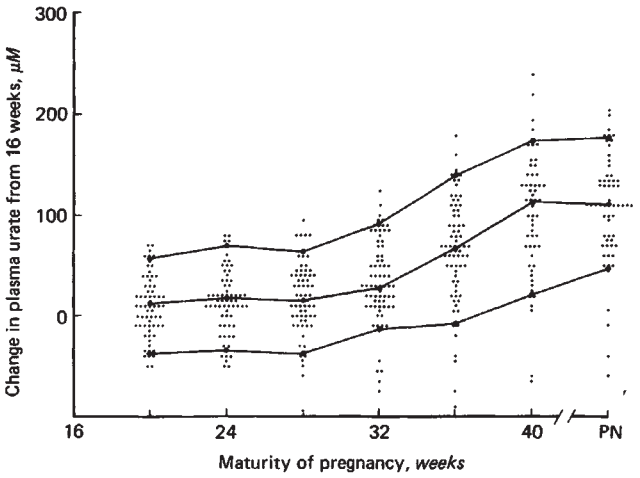

Fig. 2. *Serial changes in plasma uric acid from 16 weeks of pregnancy to 6 weeks after delivery* (PN) *were measured in a single cohort of normal primigravidae.* Plotted are the changes from the baseline reading at 16 weeks maturity. The three lines are the 10th, 50th, and 90th centiles. 100 μM of uric acid is equivalent to 1.69 mg/dl.

complicates unrecognized pre-eclampsia. In rabbits, lesions that resemble glomerular endotheliosis can be induced by DIC stimulated by infusing thromboplastins [47]; this finding lends support to the former interpretation. Furthermore, some claim that fibrin deposition in the glomeruli is a consistent feature [48], which could be the cause, rather than the consequence of, glomerular injury. But the glomerular fibrin is not found in all cases [42, 44]. Alternatively some consider that glomerular injury could be mediated by immune complexes. Immunofluorescence studies show deposition of IgM in the glomeruli [42, 49] but this feature also is not consistent [42, 44]. Further uncertainties arise because the time course of the renal biopsy changes cannot be studied in detail, and the time course of pre-eclampsia itself is poorly understood, as is its relation to placental abruption. It would be almost impossible to prove or disprove that latent pre-eclampsia preceded all cases of placental separation. This hypothesis is, however, intrinsically unlikely, because abruption is, in general, a disorder of parous women, whereas pre-eclampsia affects primiparas. Thus I conclude that renal biopsy does not provide a completely specific or sensitive diagnosis for pre-eclampsia. The heterogeneity of renal pathology and responses probably reflects the range of different maternal adaptations to placental ischemia.

Thus the clinical severity of pre-eclampsia may appear not to correlate with the degree of glomerular pathology [50]. However, in the most comprehensive study, there was a close association between the severity of the renal lesions and two other indices of the disease—retinal arteriolar spasm and hyperuricemia [45]. The relationship with hyperuricemia has been confirmed [43] and denied [41].

Hyperuricemia, a well-documented finding in pre-eclampsia, is usually an early feature [51] (Tables 2 and 3). It precedes the onset of proteinuria and hence is useful for diagnosis during the first, non-proteinuric stage. Pregnant women with chronic hypertension alone have normal plasma urate concentrations. So, a patient with both hyperuricemia and hypertension in the second half of pregnancy is more likely to have pre-eclampsia than underlying chronic hypertension, even in the absence of proteinuria, and hence to have a worse perinatal outcome [52]. Plasma urate normally rises in the third trimester (Fig. 2); as a rough guide, values above 5.0, 6.0, 7.0, and 7.5 mg/dl at 28, 32, 36, and 40 weeks, respectively, if associated with hypertension, are likely to reflect pre-eclampsia. But just as pre-existing hypertension can muddle the presentation of pre-eclamptic hypertension, so can pre-existing hyperuricemia. In addition, transient hyperuricemia during pregnancy can, as in any situation, have other causes (for example, administration of diuretics, metabolic acidosis) [53, 54]. Like most other signs of pre-eclampsia, hyperuricemia is a variable feature of the condition and sometimes may not be present even in patients with eclampsia [41].

Whether or not the pre-eclampsia is superimposed on chronic hypertension, hyperuricemia results from a reduced renal clearance of urate [55, 56]. The renal clearance of urate is reduced out of proportion to the reduced clearance of inulin [55]. Hyperuricemia can be exacerbated by eclamptic fits [57] probably because of complicating hypoxia and lactic acidosis. The

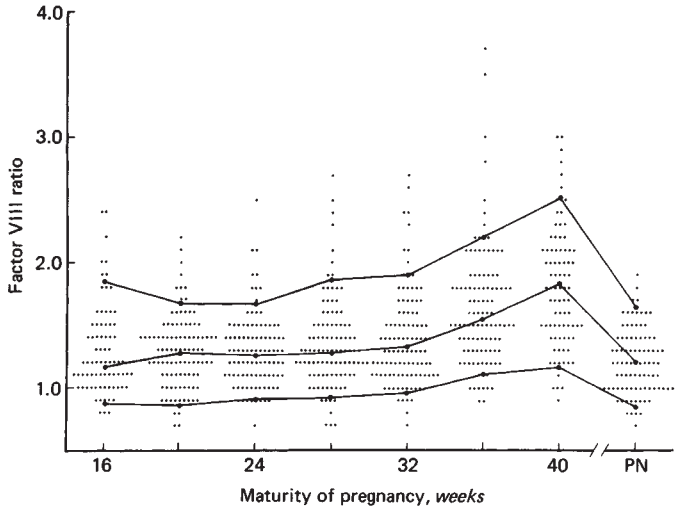

Fig. 3. *Serial changes in the ratio of plasma Factor VIII-related antigen to Factor VIII procoagulant activity were measured in a single cohort of normal primigravidae.* The expected value for non-pregnant individuals is 1.0. In normal pregnancy a slightly higher ratio is present until 32 weeks, increasing further until full term. The three lines are the 10th, 50th, and 90th centiles. Thus ratios above 2.0 at 32 weeks, 2.25 at 36 weeks, and 2.5 at 40 weeks are unusual and more typical of pre-eclampsia.

mechanisms responsible for these alterations in renal function are not defined.

In the present patient, proteinuria was associated with exacerbation of pre-existing hypertension. Initially the patient appeared to have superimposed pre-eclampsia at 23 weeks of pregnancy. If correct, the pregnancy needed to be terminated, especially because the patient had symptoms that also are encountered just prior to seizures. However, retinal arteriolar spasm and hyperuricemia both were absent. These findings supported the tentative conclusion that the underlying condition was not severe pre-eclampsia.

Secondary involvement of the clotting system

The maternal clotting system is another target for the pre-eclamptic process. In the terminally ill patient with pre-eclampsia or eclampsia, there is disseminated intravascular coagulation with gross abnormalities in hemostasis and in simple clotting tests, reflecting consumption of clotting factors and platelets. Plasma fibrin/fibrinogen degradation products are increased. The problem was first defined by autopsy studies [58], although the associated microangiopathic hemolysis had been recognized, but not explained, earlier [59].

The hypothesis that the maternal signs of pre-eclampsia are mediated by activation of the clotting system has not been substantiated. The absence of gross clotting disturbances in the majority of eclamptic women [60], or in pre-eclamptic women [61], is evidence against a primary role and demonstrates that the convulsions are not caused by DIC. However, the early stages of pre-eclampsia may be characterized by alterations in the clotting system that fall short of DIC but deviate far enough to be recognized as abnormal. The easiest to detect is thrombocytopenia [62]. Another index that frequently becomes abnormal at an early stage is the relative plasma concentrations of Factor VIII-related antigen (RA) and Factor VIII clotting activity (CA) expressed either as a ratio [63] or as a difference [64]. Both measurements are increased in normal pregnancy relative to the non-pregnant state (Fig. 3) and increase further when pre-eclampsia develops [63, 64]. These changes occur because either Factor VIII activity is destroyed by generation of intravascular thrombin or because more Factor VIII-related antigen is released into the circulation, possibly by damaged endothelium. In the patient under discussion, the platelet count and Factor VIII RA/CA ratio were normal at presentation. Both measurements remained normal until delivery, although the Factor VIII RA/CA ratio had reached the upper limit of normal for gestational age.

The cause of the disordered clotting system in pre-eclampsia is not known. Various theories include direct activation by products from a damaged placenta [65], or activation secondary to hypertensive arterial damage [60] or immunologic mechanisms [66]. Recently a more central role for platelets has been proposed. The balance between the opposing actions of thromboxane and prostacyclin may be tipped towards the proaggregating and vasoconstrictor effects of thromboxane A2 produced by platelets. There is also evidence for the production of too little prostacyclin by vascular endothelium [67] and too much thromboxane by the placental unit [68]. The effects of antiplatelet agents have been tested using aspirin [69], dazoxiben [70], or intravenous prostacyclin [71]. Two controlled trials employing low-dose aspirin [72] or low-dose aspirin with dipyridamole [73] have shown an improved outcome with treatment. These studies lend credence to the concept that platelets play a key role in the genesis of pre-eclampsia [74].

Severe thrombocytopenia in pre-eclampsia or eclampsia can be life-threatening [75], and this presentation has been confused with thrombotic thrombocytopenic purpura [76]. The combination of pre-eclamptic liver damage and thrombocytopenia produces a syndrome known by the acronym "HELLP"—hemolysis with elevated liver enzymes and low platelet counts [77].

Plasma aspartate aminotransferase (AST) activity should be measured in all patients suspected of having pre-eclampsia. Liver involvement occurs frequently, even in patients without severe hypertension or renal involvement [78]. In the present patient, liver damage was not evident at any time; this finding is consistent with the persistently normal platelet counts.

Secondary involvement of the fetus

The diagnosis of pre-eclampsia must include a detailed consideration of the fetus. Thirty years ago such a consideration extended only as far as detecting the fetal heartbeat. Now it is possible to measure fetal size accurately, estimate fetal respiratory status by heart-rate analysis, and assess uteroplacental and fetoplacental arterial flow patterns by ultrasound Doppler techniques. The uteroplacental arterial disease of pre-eclampsia and the ensuing placental dysfunction ensure that the fetus will be "compromised," particularly when the patient presents with proteinuria (stage 2) before 32 weeks of pregnancy [79]. The term "compromised" as applied to the early stages of pre-eclampsia means smaller than expected for gestational age, but it also applies to the progressive development of hypoxemia, acidosis, and asphyxiation of the fetus. Intrauterine death is a likely outcome if the fetus is not delivered in time. If delivery is delayed in unequivocal, early-onset proteinuric pre-eclampsia,

the most common outcome (after an average of 12 days, as already indicated) is progressive fetal compromise. One is then forced to choose between delivery far before term or inevitable fetal death.

In today's patient, the results of fetal assessment were normal and remained so for more than 3 months from the time of first presentation. The ultrasound measurements indicated normal fetal growth. Fetal heart-rate analysis suggested that fetal respiratory status was normal. Reassured, we considered these findings the best evidence for a diagnosis other than severe pre-eclampsia and justification for our decision to allow normal labor instead of performing an elective cesarean section. Ultrasound measurements were borne out at delivery by the finding that the birth weight was normal. The placental circulation had enough reserve to maintain fetal health through labor so that, at delivery, not only were the Apgar scores good, but the umbilical venous and arterial blood pH and gases were normal. These findings were the final, albeit indirect, proof that the spiral arteries were healthy, sustaining a normal uteroplacental circulation and fetus, and not affected by pre-eclampsia.

Summary: Principles of the diagnosis of pre-eclampsia

My central hypothesis in this discussion is that pre-eclampsia is not primarily a hypertensive or renal disorder, but a disease of pregnancy, probably of the uteroplacental arterial system. In support of this hypothesis are the following:

(*1*) Because the healthy placenta ultimately is responsible for the wide array of normal maternal physiologic adjustments to pregnancy, the ischemic placenta might be expected to cause a diverse set of systemic disturbances such as that seen in pre-eclampsia;

(*2*) None of the signs of pre-eclampsia, as currently defined, are specific for the disorder;

(*3*) The fetus is affected as well as the mother;

(*4*) The disorder cannot be understood solely in terms of the involvement of one maternal system (arterial or renal or other).

The maternal signs of pre-eclampsia comprise a diverse and highly variable set of nonspecific changes involving different organ systems; these alterations defy simple stereotyping. Without a specific test, a precise diagnosis cannot be made prospectively, nor are there any absolute criteria by which the diagnosis can be validated retrospectively.

The patient under discussion illustrates that some maternal problems can masquerade as pre-eclampsia. Despite the severity of her hypertension and the presence of proteinuria, I concluded that this patient did not have pre-eclampsia, and hence was willing to counsel continuation of the pregnancy rather than termination before fetal viability had been reached. I was persuaded to pursue this unconventional course because, in the aggregate, she did not manifest many of the more common features of the pre-eclamptic syndrome. She was not hyperuricemic, had no abnormalities of liver function, maintained a normal platelet count, and had no abnormalities of the clotting system; in addition, there were no signs of fetal growth retardation or fetal distress. Although her signs and symptoms regressed after delivery, as would also have been the case had she had pre-eclampsia, the course of the patient's next pregnancy corroborated the view that, rather than pre-eclampsia, she had had an abnormal maternal response to an otherwise normal pregnancy. Except for proteinuria, all the features that characterized the first pregnancy recurred, and again they regressed after delivery. Pre-eclampsia is predominantly a disorder of first pregnancy [80], to such an extent in fact that the proportion of nulliparae in published series has been used to "test" the validity of methods of diagnosis [50].

Finally, patients such as the one we are discussing provide evidence that the uteroplacental arteries are not unusually sensitive to maternal hypertension, and strengthen the conclusion that hypertension itself is not a mediating factor in the evolution of pre-eclampsia [81].

Questions and answers

DR. PAUL SACKS (*Renal Fellow, University of Chicago, Chicago, Illinois*): What are the mechanisms of the decreased uric acid clearance by the kidney in patients with pre-eclampsia?

DR. REDMAN: There is reduced fractional urate clearance, but the precise mechanism underlying this change is not known.

DR. MARSHALL LINDHEIMER (*Renal Section, Mitchell Hospital, Chicago*): The relative degree of intravascular hypovolemia in pre-eclampsia in comparison to normal pregnancy might be a plausible explanation for a decrement in the fractional clearance of urate. In addition, some claim that catecholamine excretion increases in pre-eclampsia, and that this rise causes a decrease in urate clearance.

DR. REDMAN: I am not convinced that either hypovolemia or catecholamine excess are adequate explanations. The degree of expansion of the plasma volume in normal pregnancy is correlated with the size of the fetoplacental unit; hence greater changes are seen with twin pregnancies, which in turn are exceeded by those occurring with triplet or quadruplet pregnancies. Conversely, pregnancies with intrauterine growth retardation are associated with a relatively contracted plasma volume whether or not pre-eclampsia is also a feature. In other words, the changes in plasma volume in pre-eclampsia may be more a consequence of fetoplacental size than of pre-eclampsia itself. Not all pre-eclamptic pregnancies are complicated by fetal growth retardation, especially when pre-eclampsia progresses rapidly. In these cases, plasma volume has not been assessed, but I would be surprised if such patients are hypovolemic, although I would expect to find hyperuricemia. The problem about invoking increased plasma catecholamines as an explanation is that some studies report increased levels, some decreased levels, and some report no changes. With this confusion I find it difficult to believe that these hormones are significant pathogenetic factors.

DR. JORDAN J. COHEN (*Chairman, Department of Medicine, Michael Reese Hospital, Chicago*): The reduction in urate clearance seems disproportionate to other manifestations of renal dysfunction. Doesn't this observation suggest that something more specific is causing the defect in tubular function in pre-eclampsia? For example, might some factor released from the placenta be interfering specifically with urate transport?

DR. REDMAN: Yes, it could. But tubular function in pre-eclampsia has never been evaluated extensively. The old theory that placental acidosis generates lactate that would compete with urate in the excretory pathways has, however, now been disproved.

DR. COHEN: You offered some circumstantial evidence that uteroplacental arterial disease is primary in pre-eclampsia; that is, histologic changes in the placenta that occur during pre-eclampsia sometimes are seen in pregnancies unassociated with hypertension. This finding suggests that these histologic changes are not secondary to hypertension. Do we know what the placental blood flow is under circumstances in which characteristic histologic changes are present, but in which pre-eclampsia is not? It seems to me that your thesis would require that placental blood flow be compromised in patients with pre-eclampsia but not in those with similar histologic changes but without hypertension.

DR. REDMAN: It is impossible to measure uteroplacental blood flow directly. Various clearance studies using radioisotope tracers have been done in the past, but they cannot be repeated because of concerns that the fetus will receive excess amounts of radiation. Arterial flow velocity patterns can be measured using ultrasound Doppler techniques. They reflect various attributes of the circulation up- and downstream of the arterial segment studied; unfortunately, flow itself cannot be deduced. The measurements about which you ask therefore have not been made. When spiral artery pathology is present without a pre-eclamptic syndrome, there is always fetal growth retardation. This observation suggests that uteroplacental flow is reduced regardless of whether maternal hypertension is present.

DR. BRIAN DUFFY (*Attending Nephrologist, Michael Reese Hospital*): When nephrotic patients become pregnant, one of the important signs of pre-eclampsia—the onset of proteinuria—is obscured. Could one use the selectivity of the proteinuria in these patients as a guide?

DR. REDMAN: I know of no study that provides a baseline for such an approach to clinical management. However, I believe that even in the patient with nephrotic syndrome the principles of diagnosing pre-eclampsia are still the same except that an increment in proteinuria is sought, in association with the other possible signs of superimposed pre-eclampsia. Quantifying protein excretion generally is simpler than measuring selectivity of proteinuria.

DR. SUSAN HOU (*Renal Section, Michael Reese Hospital*): Would you comment on your use of nifedipine in this patient and in other pre-eclamptic patients?

DR. REDMAN: We have used nifedipine for the treatment of pre-eclamptic hypertension as a second-line drug to methyldopa. In our limited experience it appears to be safe, but we do not regard its safety for the fetus as entirely proven. It certainly has advantages over both hydralazine and diazoxide. We do not use magnesium sulfate to treat our patients, and any possible interaction between this agent and nifedipine has not been examined.

DR. COHEN: Does aggressive treatment of the hypertension alter the natural history of pre-eclampsia?

DR. REDMAN: No, except insofar as it can help prevent cerebral hemorrhage. In this respect medical treatment is an adjunct to the definitive management, which is always delivery. All the evidence suggests that the disorder begins and develops independently of the blood pressure, which is a secondary sign of some other, more fundamental, process.

DR. ARNOLD BERNS (*Attending Nephrologist, Michael Reese Hospital*): Would you comment in more detail on the recent data suggesting that low-dose aspirin is useful for prophylaxis of pregnancy-induced hypertension and pre-eclampsia?

DR. REDMAN: This treatment is based on investigations which show that the disorder is associated with a deficiency of prostacylin release from the arterial wall and an excess production of thromboxane. There have been two trials. In the first, Beaufils used aspirin combined with dipyridamole in a heterogeneous group of high-risk, mainly parous women [73]. He showed a modest benefit after starting treatment early in the second trimester. The second trial was more precise in that the subjects, all of whom were primigravidas, were selected on the basis of an angiotensin infusion test. Only those who showed an excess response were selected for randomization either to low-dose aspirin (without dipyridamole) or placebo [72]. Again the aspirin therapy, started at 28 weeks of pregnancy, was associated with benefit in terms of the eventual outcome. We need further, much larger trials, to test low dose-aspirin under conditions that more closely correspond to ordinary clinical practice. If these studies showed the same sort of benefit, then for the first time we would have a medication that would change the outcome of this condition.

DR. FREDRIC COE (*Renal Section, Mitchell Hospital*): Do I understand correctly that you regard pre-eclampsia as a syndrome in which the spiral arteries must always be involved and that that is the basis for classifying a patient as having pre-eclampsia? Or is the basis that some complex of findings must reach a critical threshold? This woman clearly was excluded from the diagnosis, perhaps because her baby did well. Could you clarify the current definitive basis for calling someone a victim of pre-eclampsia?

DR. REDMAN: Yes; I regard pre-eclampsia as a disorder of the placenta, a consequence of poor placentation. Poor placentation, amongst other changes, prevents the spiral arteries from dilating and thus providing the uteroplacental blood flow necessary for the second half of pregnancy. The major physiologic changes of pregnancy are due to the presence of a healthy placenta in the uterus. Pre-eclampsia, I believe, represents the aggregate of changes caused by the presence of a sick (ischemic) placenta. I find this a useful model, one that explains all that I see in my clinical practice. I do acknowledge that proof of its correctness is lacking.

Developing a precise definition of pre-eclampsia at present may have the merit of achieving linguistic uniformity, but it blocks further evolution of thought about one (or several) poorly understood disorders of pregnancy. We are in the common situation where arguments arise because of a lack of knowledge. In this presentation, I have put forward a working hypothesis that was helpful in the management of this patient. To me this hypothesis has been tested under difficult circumstances and found to be adequate. Clearly more definitive information is urgently needed.

DR. COE: To reiterate, what we must look for in clinical practice, if we are to consider the diagnosis of pre-eclampsia, is a hypertensive syndrome in association with evidence that the fetus is doing poorly. I am trying to clarify, at least from a clinical point of view, when we would dare take the chances that you took with the patient under discussion.

DR. REDMAN: No, this is not what I mean. Pre-eclampsia has, if you like, two components—maternal and fetal—occurring together in highly variable combinations of severity. The

fetal component, that is, smallness with or without evidence of respiratory insufficiency, is usually but not invariably present. In some cases, the maternal component apparently is disproportionately severe relative to the fetal. The converse also can happen; that situation is more familiar to obstetricians than to internists. In the patient we have discussed today, the maternal component was not convincingly pre-eclampsia, because neither hyperuricemia nor involvement of the clotting system was present. The absence of a fetal component provided strong, but not perfect, supporting evidence that the patient did not have pre-eclampsia. But in terms of clinical practice it is not possible to "exclude" pre-eclampsia simply because the fetus appears to be uninvolved. If the fetus does appear to be normal, however, the other conditions that can masquerade as pre-eclampsia must be considered seriously.

DR. ALAN SEGAL (*Medical Resident, Michael Reese Hospital*): You have theorized that pre-eclampsia is a disease of the uteroplacental junction, specifically of the spiral arteries, and you have noted that some patients have normal renal biopsies, which I presume includes the absence of fused podocytes on electron microscopy. Given this observation, what is the cause of the proteinuria in pre-eclampsia?

DR. REDMAN: In pre-eclampsia the foot processes of the renal glomeruli are intact. So the mechanism of the proteinuria relates to a different process that has yet to be defined. As I mentioned, if a pregnant woman has an acute abruption, and her clotting system is activated, she will develop changes in her renal biopsy and proteinuria. One theory is, therefore, that the proteinuria is the consequence of fibrin deposition in the glomeruli.

DR. LINDHEIMER: The failure of trophoblasts to invade the spiral arteries, which thus don't "dilate," as well as the uterine ischemia theory of pre-eclampsia ought to be very appealing to nephrologists. In essence we convert the "Goldblatt kidney" model of hypertension to a "Goldblatt uterus." Unfortunately, not all the data in the literature support this view. Of greatest interest is the series of observations from the group at Parkland Hospital in Dallas. These data suggest that placental blood flow is actually increased early in the course of gestation in individuals who subsequently develop pre-eclampsia, and only decreases when overt disease occurs. These observations were based on the use of the placental clearance of dehydroisoandrosterone sulfate, androstenedione, etc. as "indices" of placental blood flow [82].

Another point that deserves focus in our discussion is the concept of temporizing when a patient, such as the one discussed today, presents with severe hypertension at 23 weeks. In your presentation you alluded to the fact that most authorities agree that changes in the coagulation system or evidence of hepatic dysfunction, such as elevated transaminase levels, are danger signs of potential maternal disaster. Also, if we are secure at 23 weeks that the patient has superimposed or pure pre-eclampsia, fetal outcome is so poor even with temporization that risks to the mother preclude continuation of the pregnancy. In both instances, therefore, we would terminate the gestation. Many of us also would worry about continuing pregnancy in a mother when one cannot successfully control her blood pressure. For instance, one may see the complications of hypertension in the fundi at lower mean blood pressures during gestation compared with nongravid populations. There is also a higher incidence of cerebral vascular accidents when blood pressure is high during pregnancy. I think it is fair to say that currently any mortality or any form of residual morbidity in a young mother attributable to hypertension in pregnancy is unacceptable. This is probably the reason for the aggressive intervention tactics of fetal-maternal experts, sometimes to the surprise of my fellow nephrologists and internists. Would you comment on this?

DR. REDMAN: The studies you cite did not measure uteroplacental blood flow directly. Altered hormone clearances might have reflected hypoxia-induced proliferation of trophoblast. I do not think, therefore, that the data from Texas are difficult to accommodate within the hypothesis that I have described.

With regard to the second part of your question, I agree that any mortality or residual morbidity resulting from a system of management of hypertension in pregnancy is unacceptable. It cannot be emphasized too much that the patient presented today is *not* an example of how to manage proteinuric pre-eclampsia (that is, stage 2 or stage 3) at 23 weeks of gestation, or indeed at any other time. If that had been the diagnosis, the correct management would have been termination of the pregnancy, because we know that we can expect only 12 days of extra time, on average, by temporizing. The decision not to deliver was justified only in terms of our conviction that she did not have pre-eclampsia. My purpose in presenting the case was to show how this conclusion was reached, how it was tested, and how it led to two successful pregnancies without ensuing morbidity. The patient was extremely unusual, and it is improbable that we shall encounter another like her. Therefore, the message concerns not so much the details of management, but the conceptual approach to thinking about, and dealing with, pre-eclampsia.

DR. COHEN: What is the long-term prognosis for women who experience a pre-eclamptic pregnancy?

DR. REDMAN: A pre-eclamptic illness can provoke irreversible events such as renal cortical necrosis, cerebral hemorrhage and infarction, or retinal detachment, which can lead to permanent morbidity. The evidence from long-term followup studies shows that, if these events do not happen, then those who were pre-eclamptic as primigravidas enjoy a normal life expectancy. Those who suffer pre-eclampsia in second or later pregnancies have a higher incidence of cardiovascular disease in later life and a reduced life expectancy.

DR. COHEN: Is the incidence of pre-eclampsia falling?

DR. REDMAN: The National Perinatal Surveys in 1958 and 1970 looked at unselected samples of deliveries in England and Wales. Both studies used the same diagnostic criteria, and the incidence of pre-eclampsia was similar in both surveys.

Reprint requests to Dr. C. W. G. Redman, John Radcliffe Hospital Maternity Department, Headington, Oxford OX3 9DU, England

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