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Edema associated with low plasma protein level and any gestational hypertension as warning signs of HELLP syndrome

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ABSTRACT

Purpose: Because preeclampsia is a multisystem disorder, its definition has recently been revised, including cases with evidence of renal, liver, neurological, or hematological dysfunction. However, the role of edema remains unclear. While the presence of mild edema is common in normal pregnancy, in severe preeclampsia protein transfer from the vascular into the interstitial compartment could lead to low serum protein level and favor the transport of fluid to the interstitial compartment.

Materials and methods, Results: Over a 4-year period, 9749 women have given birth in our university maternity ward. In this period of time, 86 women developed severe preeclampsia. Among them, we retrospectively identified nine patients who first presented with mild de novo hypertension or preeclampsia, extensive edema or excessive gestational weight gain (GWG), and documented low serum protein levels; five patients also reported headache. Serum protein levels ranged from 51 to 56 g/l. We analyzed the progression of the disease in these women, and found that these patients developed criteria for complete or partial hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome in four and five cases, respectively. All patients were delivered quickly of healthy babies, and no other maternal adverse outcomes occurred.

Discussion: As plasma proteins are the primary determinants of plasmatic colloid osmotic pressure (COP), headache in association with edema, low serum protein levels, and even mild hypertension, could reflect cerebral vasogenic edema with the same mechanism as for cerebral edema reported in posterior reversible encephalopathy syndrome and eclampsia. Thus, the sequential association of edema or excessive GWG with markedly low serum protein levels and mild gestational hypertension could signal the imminent development of severe preeclampsia and possibly HELLP syndrome. This sequence should be assessed in additional large-scale prospective studies.

Abbreviations: GWG: gestational weight gain; HELLP: hemolysis, elevated liver enzymes, and low platelet count

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Edema; gestational weight gain; headache; severe preeclampsia; HELLP syndrome; pregnancy-induced hypertension; low serum protein level

Background

Because preeclampsia is a multisystem disorder, its definition has recently been revised, including cases with evidence of renal, liver, neurological, or hematological dysfunction [1–3]. However, the role of edema and/or excessive gestational weight gain (GWG) as a warning sign and in the pathophysiology of preeclampsia remains unclear. Indeed, the presence of mild edema is common and considered as benign during normal late pregnancy, and only the sudden occurrence of significant swelling is considered to be

of concern, particularly when it occurs in the hands and the face. While the presence of mild edema is common in normal pregnancy, in severe preeclampsia protein transfer from the vascular into the interstitial compartment has been reported [4], which favors the transport of fluid to the interstitial compartment, leading to greater edema in relation to lower colloid osmotic pressure in plasma (COP_p) [4]. As plasma proteins are the primary determinants of COP_p, an excellent correlation has been reported between COP_p and the total serum protein levels [5].

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Patients and methods

All pregnant women booked to deliver in our university hospital are informed that data are routinely entered at birth into an electronic record-keeping system, then checked during the maternity stay of each woman by a midwife qualified in data management and storage for contributions to the national "Programme de médicalisation des systèmes d'information" (PMSI) database. They are also informed that indicators of perinatal health are regularly analyzed to assess the overall quality of obstetric care and to update medical management protocols and publication of research results. The database has been declared to the French data protection authority (*Commission Nationale de l'Informatique et des Libertés* [CNIL]). Over a 4-year period, 9749 women have given birth in our university maternity ward. In this period of time, 86 women developed severe preeclampsia. Among them, we retrospectively identified nine patients who presented with mild hypertension or preeclampsia without classic severe features, extensive edema or excessive GWG, and documented low serum protein levels which ranged from 51 to 56 g/l (Table 1). In five patients, headache was also reported. We analyzed the progression of the disease in these women, and found that all nine patients developed thrombocytopenia, elevated serum aminotransferase and/or lactate dehydrogenase, later fulfilling criteria for complete (patients 4, 5, 6, and 7) or partial (patients 1, 2, 3, 8, and 9) hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (Table 1). All patients were delivered of healthy babies, and no other maternal adverse outcomes occurred.

Discussion

Mild edema can be a common symptom in uneventful pregnancies with normal outcomes. But in these nine

cases with the onset of mild hypertension or preeclampsia in association with edema and/or excessive GWG and low serum protein levels, which ranged from 51 to 56 g/l, a quick progression toward severe preeclampsia was observed, including thrombocytopenia, elevated serum aminotransferase, and/or lactate dehydrogenase, constituting complete or partial HELLP syndrome.

In actuality, in severe preeclampsia, increased microvascular protein permeability with lower serum protein levels and COP_p , has been reported, which favors protein transfer and the transport of fluid from the vascular into the interstitial compartment [4]. Thus, the association of edema with low serum protein level and even mild hypertension could be a warning sign. Especially, in HELLP syndrome, hypertension is mild in 15–50%, absent in 12–18% of cases, and no proteinuria is reported in 13% of cases [6,7]. In those cases of HELLP syndrome without or with only mild clinical symptoms, diagnosis and adequate management may be delayed, leading to adverse outcomes [6,7]. Therefore, given the potential for the rapid progression and serious complications of this condition, any clinical or biological indication that may predict HELLP syndrome deserves prompt recognition to support timely management.

From a pathophysiological point of view, the earliest change in pregnancy is primary systemic arterial vasodilation associated with sodium and water retention as the plasma osmolality decreases, which causes arterial underfilling and a compensatory 30–50% increase in blood volume [8–11]. A reduction in the COP in both the interstitial fluid (COP_i) and COP_p physiologically restricts the increase in interstitial fluid volume and edema formation in normal late pregnancy [4]. Indeed, the COP_p was found to be reduced in normal pregnancy from the first to the third trimester, but concomitantly, the COP_i decreased even more

Table 1. Clinical and biological characteristics of the patients.

	Age	Mode of delivery	WG + d	Obstetric history	GWG, edema	Platelets (cells/ μ l), AST (IU/l)/ALT (IU/l), LDH (IU/l)	Proteinemia (g/l)	Symptoms
Patient 1	39	VD	39	0	9 Edema	92,000, 110/26, 1474	51	Headache, preeclampsia
Patient 2	26	VD	33	0	18	172,000, 473/512, 823	52	Headache, hypertension
Patient 3	41	Cs	38 + 5	One PUP	12 Edema	143,000, 549/656, 864	51	Preeclampsia, then eclampsia
Patient 4	30	CS	39	0	20	46,000, 305/212, 1423	55	Epigastric pain, hypertension
Patient 5	24	VD	35 + 6	0	17 Edema	97,000, 392/312, 855	52	Preeclampsia
Patient 6	36	Twin Cs	37	0	15 Edema	68,000, 277/207, 1569	56	Headache, preeclampsia
Patient 7	32	VD	38	One PUP	19	94,000, 504/177, 2619	54 Alb 26	Headache, preeclampsia
Patient 8	31	Cs	35	One PUP	15 Edema	90,000, 46/40, 580	54	Headache Preeclampsia,
Patient 9	40	CS	37	0	20	124,000, 128/180, 570	53	Preeclampsia

To meet diagnostic criteria of HELLP syndrome [1], liver transaminases (AST, ALT) should be elevated >70 IU/l (more than twice the upper limit of normal), total serum lactate dehydrogenase (LDH) should be 600 IU/l or more, and the platelet count should be $<100,000/\text{mm}^3$. Lactate dehydrogenase elevated to 600 IU/l or more, aspartate aminotransferase and alanine aminotransferase elevated more than twice the upper limit of normal, and platelet count below 100,000/mm.

GWG: gestational weight gain; PUP: previous uneventful pregnancy; VD: vaginal delivery; Cs: cesarean section; WG + d: weeks of gestation + days; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase

[10,11]. In moderate pre-eclampsia the reduction in COP_p may also be compensated for by a similar reduction in the fluid $COPI$ due to either increased lymphatic protein “washdown” or by the dilution of interstitial proteins caused by the transcapillary transudation of protein-poor fluid [10,11]. In contrast, in severe preeclampsia, increased microvascular protein permeability with protein transfer in the interstitial compartment favors the transport of fluid from the vascular to the interstitial compartment, leading to extensive edema and excessive GWG [4,10,11].

We also observed headache in five of nine patients, in association with mild hypertension, edema, and low serum protein level, preceding the onset of HELLP syndrome, and then the clinical biological profile progressed toward severe preeclampsia with partial or complete HELLP syndrome. The significance of headache for management of hypertensive disorders in pregnancy was recently revisited [1–3]. Headache may be considered either a symptom of severe hypertension or a true feature of severe preeclampsia in itself and was reported by 31–61% of patients with HELLP syndrome in several large series [6,7]. The role of headache in the classification and management of hypertensive disorders of pregnancy was recently highlighted, since “new-onset cerebral or visual disturbances” were included as one of six features of severe preeclampsia by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [1] and the American College of Obstetricians and Gynecologists [2,3]. Some researchers have even proposed detailed guidelines for the evaluation and management of pregnant women with headache [12]. The transport of fluid from the vascular to the interstitial compartment which reflects in low plasma protein level [5], may also underlie vasogenic edema with the same mechanism as for cerebral edema reported in posterior reversible encephalopathy syndrome and eclampsia [12,13]. Hecht et al. [14] recently identified from 317 autopsies of women who died of eclampsia not only “brain perivascular edema” (68.4%), which was unsurprising, but also liver lesions characterized by “periportal hemorrhage and dilation of the sinusoids” (72.2% in this series) as the predominant problems. The presence of HELLP syndrome is also characterized by impaired capillary perfusion [15] and increased permeability to plasma proteins, and it may be linked to cerebral edema [15–18].

Conclusions

Overall, we observed in our study that the sequential association of edema or excessive GWG with markedly

low serum protein levels and even mild gestational hypertension could signal the imminent development of severe preeclampsia with HELLP syndrome features. This sequence should be assessed in additional large-scale prospective studies.

Ethics approval and consent to participate

All pregnant women booked to deliver in our university hospital are informed of the follow-up schedule and that perinatal data (excluding individual details, images or videos) are routinely entered at birth into an electronic record-keeping system for contributions to the mandatory national “Programme de Médicalisation des Systèmes d’ Information” (PMSI) database. Written informed consent is obtained from all women, and the database has been declared to the French data protection authority (*Commission Nationale de l’Informatique et des Libertés* [CNIL]).

This short report is a retrospective description of clinical biological findings obtained from this database during the observed course of events that document an undescribed aspect of the course of the severe preeclampsia. There was no hypothesis testing and no systematic data collection beyond that which was part of routine clinical practice, and the dataset used in the present case series is fully anonymous, containing the minimum level of detail necessary to reproduce clinical items and all numbers reported in the paper, without any identifying features, providing to patients the highest degree of confidentiality.

Disclosure statement

The authors declare that they have no competing interests.

Author contributions

LC: Study conception and design; LC and JB: Analysis and interpretation of data; LC: Drafting of manuscript.

Data availability statement

All data analyzed and used in the study may be shared with other researchers on request provided the data comply with the same standards as the main dataset.

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