

# A randomized trial comparing low-dose combined spinal-epidural anesthesia and conventional epidural anesthesia for cesarean section in severe preeclampsia

N. BERENDS, A. TEUNKENS, E. VANDERMEERSCH, M. VAN DE VELDE

**Abstract :** *Background and objectives :* A prospective, randomized study was designed to compare the maternal and neonatal effects of conventional epidural anesthesia and combined spinal epidural anesthesia (CSE) for Cesarean section in severe preeclamptic patients. Additionally, two strategies in the prophylactic management of hypotension in severe preeclamptic patients were evaluated: fluid preloading or prophylactic ephedrine.

*Methods :* Thirty nonlaboring women with severe preeclampsia (PET), scheduled for an elective Cesarean section, were randomised into three groups: epidural anesthesia with prophylactic fluid loading (EA-F), combined spinal epidural anesthesia with prophylactic fluid loading (CSE-F), or combined spinal epidural anesthesia with prophylactic ephedrine (CSE-V). Hemodynamic data were recorded prior and after induction of regional anesthesia at five-minute intervals. The total amount of intravenous administered fluid and the total dose of vasopressors were recorded.

*Results :* Hemodynamic data were similar between the three groups. The incidence and duration of hypotension was similar in all three groups. Significantly more ephedrine was used in the CSE-V group as compared to the CSE-F group. More lactated Ringer's solution was used in the CSE-F group as compared to the CSE-V group. There were no hypertensive episodes and none of the patients developed pulmonary edema. The time period from induction until the start of surgery and the duration of surgery were significantly shorter in both CSE-groups. Neonatal outcome was comparable between the three groups.

*Conclusion :* Our results confirm that combined spinal and epidural anesthesia (CSE) is a safe alternative to conventional epidural anesthesia in severe preeclamptic women and that the prophylactic use of ephedrine is effective and safe to prevent and treat spinal hypotension after combined spinal and epidural anesthesia for Cesarean section in severe preeclamptic women.

**Key words :** Combined spinal epidural anesthesia; epidural anesthesia; fluid preloading; hypotension; prophylactic vasopressor; severe preeclampsia.

## INTRODUCTION

Preeclampsia and eclampsia are leading causes of maternal morbidity and mortality. It occurs in about 6% of all pregnancies and 5-10% of these cases are severe. The mortality rate is still 7.5 per million maternities (1). The need for cesarean delivery in (severe) preeclamptic patients is much higher than in the healthy pregnant population. A safe, reliable and fast anesthesia technique is desired when a (semi-urgent or urgent) cesarean delivery is needed. General anesthesia is fast and reliable but can, especially in preeclamptic patients, be associated with intubation problems and a significant hypertensive response to intubation, which can lead to cerebral edema or intracranial hemorrhage, pulmonary edema and myocardial ischemia.

Spinal anesthesia can provide reliable and fast anesthesia but its use is controversial in severe preeclamptic patients. Surgical anesthesia to the level of T4 is necessary to provide an adequate block for cesarean section. As a consequence rapid, complete sympathetic block occurs, resulting in hypotension and decreased cardiac output (2).

Because the preeclamptic patient has a reduced plasma volume, many fear that the risk of hypotension induced by the sudden sympathetic blockade is higher than in healthy pregnant women

N. BERENDS, M.D.; A. TEUNKENS, M.D.; E. VANDERMEERSCH, M.D., PH.D.; M. VAN DE VELDE, M.D., PH.D.

Department of Anesthesiology, University Hospitals Gasthuisberg, Katholieke Universiteit Leuven, Herestraat 49, B-3000 Leuven, Belgium.

**Correspondence address :** M. Van de Velde, Director Obstetric Anesthesia and Extra Muros Anesthesia, Department of Anesthesiology, University Hospitals Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

Tel. : 0032-16 34 42 70. Fax : 0032-16 34 42 45.

E-mail : marc.vandvelde@uz.kuleuven.ac.be.

and higher than in patients treated with epidural anesthesia. Hypotension may result in decreased uteroplacental perfusion and thus in a compromised fetus. The availability of the combined spinal epidural (CSE) technique has the advantage that small doses of spinal anesthetics are possible and the presence of the epidural catheter provides the flexibility to extend the level and the duration of the block. Recent studies show a similar (3-13) or even a reduced (14) incidence of hypotension after CSE or spinal anesthesia in preeclamptic patients, as compared to epidural anaesthesia. Unfortunately studies are often retrospective or performed in mild preeclamptic patients.

The pathophysiology of preeclampsia is characterized by widespread vasoconstriction, marked reductions in plasma volume, increased uterine vascular resistance resulting in 40% less uterine blood flow, a hyperdynamic cardiovascular state with a high cardiac index, and decreased plasma oncotic pressure. This makes the preeclamptic patient at risk for iatrogenic pulmonary edema when excessive fluid loading is given and for hypertensive crises, when vasopressors are aggressively being administered (15, 16).

We designed a prospective, randomized study to compare CSE anesthesia and conventional epidural anesthesia in severe preeclampsia. Additionally, we tested two strategies for prophylaxis of hypotension in severe preeclamptic patients requiring regional anesthesia for cesarean section: fluid preloading or prophylactic ephedrine.

## METHODS

Following institutional ethical committee approval and written, patient, informed consent, 30 severe preeclamptic patients scheduled for non-emergent cesarean section were enrolled in the study. Patients presenting for urgent cesarean section, parturients in active labor, patients with coagulation disorders and twin pregnancies were excluded.

Preeclampsia is defined as sustained values of blood pressure of at least 140 mmHg systolic and 90 mmHg diastolic, the presence of proteinuria (> 300 mg of protein in a 24 hour urine collection or the finding of + or ++ on semi quantitative analysis by dipstick in two midstream samples taken more than 6 hours apart) and a gestational age of more than 20 weeks. Severe preeclampsia is defined as preeclampsia combined with one of the following conditions (17): severe hypertension

(sustained blood pressure of at least 160 mmHg systolic or at least 110 mmHg diastolic on at least two occasions 6 hours apart), severe proteinuria (> 5 g of protein in a 24 hour urine collection or the finding of 3+ or 4+ on semi quantitative analysis by dipstick on two midstream samples taken more than 6 hours apart), oliguria (< 400 ml over 24 hours), cerebral or visual disturbances, pulmonary oedema, epigastric pain, hepatic rupture, impaired liver function, thrombocytopenia, HELLP syndrome and evidence of fetal compromise.

The patients were randomly assigned to three groups with 10 patients in each group. In group 1 conventional epidural anesthesia was performed (EA-F group). In the second and third groups CSE anesthesia was performed. In group 2 (CSE-F group) prophylactic fluid loading was performed. In group 3 (CSE-V group) no fluid loading was given but prophylactic ephedrine was administered.

In group 1, following IV fluid load with 10 mL/kg lactated Ringer's, epidural anesthesia was performed at the L3-L4 lumbar interspace with the patient in the sitting position using an 18-gauge Tuohy needle. The epidural space was identified using the loss of resistance to saline technique and an epidural catheter was advanced into the epidural space. The catheter was tested by injection of 3 mL of xylocaine 1% with adrenaline 1/800.000. Anesthesia was induced using ropivacaine 0.5% combined with sufentanil 1 mg/mL. The volume of the ropivacaine /sufentanil mixture administered to the patient depended on the height of the patient: 0.8 mL of the mixture was injected for every 10-cm of the patient's height. Anesthesia was induced with the patient placed in the supine position with left lateral tilt. All patients received 6 L of oxygen via face mask. In the CSE-F and CSE-V groups combined spinal epidural anesthesia was performed with the patient in the sitting position at the L3-L4 vertebral interspace. Following identification of the epidural space using the loss of resistance to saline technique, a 27 G Whitacre spinal needle was advanced through the dura. Following gentle aspiration of cerebrospinal fluid, sufentanil and hyperbaric bupivacaine were administered intrathecally. Hyperbaric bupivacaine 7.5 mg and 2.5 µg sufentanil were dissolved a volume of 2 mL. From this mixture 0.1 mL/10 cm of the patients height was given intrathecally. An 18 G epidural catheter was then inserted into the epidural space following removal of the spinal needle.

In both the CSE-F and EA-F groups prophylactic Ringer's lactate 10 mL/kg was given intravenously ten minutes prior to initiation of

anesthesia. No vasopressors were given prior to initiation of anesthesia. In the CSE-V group no IV fluids were given but prophylactic ephedrine 15 mg was given during initiation of the spinal block. Parallel with the injection of the intrathecal drugs, an infusion of 150 mL of lactated Ringer's solution was administered intravenously over 5' in which 15 mg of ephedrine was dissolved.

Hypotension was defined as a reduction of mean arterial pressure of more than 15% of the baseline value. When hypotension developed, an additional bolus of lactated Ringer's solution (5 mL/kg) was infused in the CSE-F and EA-F groups. If hypotension persisted, hydroxyethylstarch 6% (HAES ; 5 mL/kg) was administered. If this too was unsuccessful, 5 mg of ephedrine was given intravenously in repeated doses until blood pressure was restored to within normal limits or until a total dose of 50 mg ephedrine was administered. If hypotension still persisted after 50 mg of ephedrine, phenylephrine was given per 100 µg intravenously.

If hypotension developed in the CSE-V group, 5 mg of ephedrine was given intravenously in repeated doses until blood pressure was restored to within normal limits or until a total dose of 50 mg ephedrine was administered. If hypotension still persisted after 50 mg of ephedrine, phenylephrine was given per 100 µg intravenously.

A block to a level of T2 using ether swabs as a cold discrimination test or a block to T4 using pinprick is typically used as the block height at our institution to perform Cesarean section.

If after 20 minutes the upper level of anesthesia failed to reach dermatome T4 (determined by sensitivity to pinprick) or T2 (determined by sensitivity to ether swabs), epidural ropivacaine 0.5% was administered. The volume of the extra dose was determined by the upper level of anesthesia : 1 mL of the mixture per unblocked segment until the upper level reaches T4 (determined by sensitivity to pinprick).

Heart rate and oxygen saturation were continuously monitored. Blood pressure was measured automatically at 2.5 minute intervals.

Data collection includes demographic variables, proteinuria, platelet count, liver function, uric acid, volume of intra-operative administered fluids, total intra-operative administered ephedrine, time from induction of regional anesthesia to start of cesarean section, duration of surgery, total blood loss, need for supplemental analgetics (intravenous and/or epidural), blood pressure and heart rate at 30-min before induction of regional anaesthesia (baseline) and with a 2.5 minute interval during the

first hour after induction of regional anaesthesia. Apgar scores, at 1, 5 and 10 minutes, and umbilical blood gases were measured after delivery.

Data are compared according to the anesthetic technique used and the protocol used to treat hypotension.

Our primary outcome variable is the incidence of hypotension. A power analysis revealed that we needed to include ten patients in each group to demonstrate a 70% difference in the incidence of hypotension between the groups with a power of 80% and a 5% significance level. All data were analysed using Chi-square analysis or analysis of variance (ANOVA) with Scheffe's post-hoc test whenever appropriate. A p-value < 0.05 was considered significant.

## RESULTS

Demographic and obstetric data are presented in table 1 and table 2. No differences between the groups were identified. In all patients epidural or combined spinal-epidural anesthesia was performed successfully and no conversion to general anesthesia was required.

Intra-operative data revealed a significantly shorter time period from induction until the start of surgery and a shorter duration of surgery in both CSE-groups. Blood loss was similar in the three groups (Table 3). Seven patients in the epidural group needed supplemental analgesics (6 epidural and 1 intravenous supplement), whereas only two patients in the CSE-groups needed supplemental epidural analgetics (one in each group).

The baseline mean arterial pressure (MAP) was higher in the EA-F group but the difference was not significant and MAP remained comparable between the groups during surgery

(Fig. 1). After induction of CSE, MAP was stable in the two CSE groups (Fig. 1).

Maternal heart rate was not significantly different during the study period between the groups. There were no episodes of maternal tachycardia or bradycardia.

Hypotensive episodes occurred frequently (5 episodes vs 8 and 6, NS) and in a similar number of patients (5 vs 4 and 6, NS) in the EA-F, CSE-F and CSE-V groups respectively. Duration of hypotension was not significantly different ( $2.5 \pm 2.6$  vs  $6.5 \pm 9.1$  and  $4.5 \pm 6.1$  minutes) between the three groups and in none of the groups extreme hypotension (defined as a reduction of more than 30%) occurred (Table 4).

Table 1  
Demographic Data

	EA-F	CSE-F	CSE-V	p-value
Age (yr)	28 ± 7	29 ± 4	33 ± 4	NS
Height (cm)	167 ± 2	166 ± 7	163 ± 9	NS
Weight (kg)	85 ± 10	74 ± 20	85 ± 12	NS
Gestational age (wk)	34.1 ± 2.6	35.0 ± 2.6	35.8 ± 1.7	NS

All data are presented as mean ± Standard Deviation. p-value versus EA-F group.

EA-F : epidural group ; CSE-F : combined spinal epidural group treated with fluids ; CSE-V : combined spinal epidural group treated with vasoconstrictors.

Table 2  
Baseline Bloodwork Results

	EA-F	CSE-F	CSE-V	p-value
Platelet counts (*10 <sup>9</sup> )	159 ± 71	190 ± 62	189 ± 61	NS
Proteinuria (mg/L)	3828 ± 5014	4445 ± 1223	2330 ± 4043	NS
Uric acid (mg/dl)	7.6 ± 2.2	6.8 ± 1.5	6.9 ± 1.9	NS
ALT (U/L)	35 ± 36	33 ± 55	25 ± 19	NS
AST (U/L)	40 ± 33	44 ± 65	30 ± 23	NS
LDH (U/L)	375 ± 258	455 ± 110	432 ± 260	NS
Bilirubin (mg/dl)	.34 ± .17	.52 ± .31	.40 ± .35	NS

All data are presented as mean ± Standard Deviation. p-value versus EA-F group.

EA-F : epidural group ; CSE-F : combined spinal epidural group treated with fluids ; CSE-V : combined spinal epidural group treated with vasoconstrictors.

Table 3  
Surgical Data

	EA-F	CSE-F	CSE-V	p-value
Time to incision (min)	28.5 ± 7.8	9.5 ± 4.4	9.1 ± 3.6	< 0.00001
Duration of surgery (min)	89.5 ± 14	63 ± 12	51 ± 12	< 0.001
Blood loss (ml)	560 ± 163	540 ± 395	690 ± 256	NS

All data are presented as mean ± Standard Deviation. p-value versus EA-F group.

EA-F : epidural group ; CSE-F : combined spinal epidural group treated with fluids ; CSE-V : combined spinal epidural group treated with vasoconstrictors.

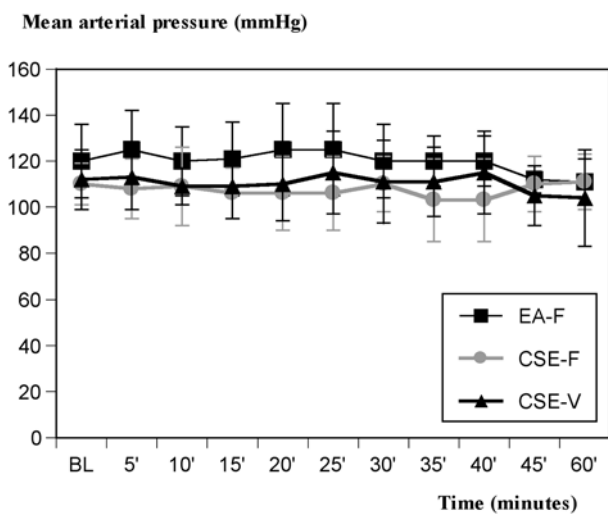


Fig. 1. — Mean arterial pressure in the three study groups during the first hour after anesthetic induction. All data are presented as mean ± Standard Deviation. No statistically significant differences between the groups were identified.

As expected more ephedrine ( $28 \pm 16$  vs  $0 \pm 0$  and  $0 \pm 0$  mg,  $p < 0.05$ ) and less lactated Ringer's solution ( $678 \pm 65$  vs  $1605 \pm 270$  and  $1680 \pm 380$  mL,  $p < 0.05$ ) were administered in the CSE-V group (Table 4) as compared to the EA-F and CSE-F groups. None of the patients needed a rescue dose of phenylephrine (Table 4). There were no hypertensive episodes in the three groups.

Neonatal data (Table 5) showed a significantly lower birth weight in the EA-F group ( $p < 0.03$ ). There were no significant differences in Apgar scores, umbilical arterial and venous pH or umbilical arterial base deficit. The number of neonates who needed admission to the neonatal unit (NU) was not significantly different between groups (5 vs 5 and 2).

None of the mothers developed pulmonary edema and none of them needed admission to the ICU. There was no report of symptoms consistent

Table 4  
Hemodynamic Data

	EA-F	CSE-F	CSE-V	p-value
Episodes of hypotension (n)	5	8	6	NS
Patients with hypotension (n)	5	4	6	NS
Duration of hypotension (min)	2.5 ± 2.6	6.5 ± 9.1	4.5 ± 6.0	NS
Episodes >30% reduction	0	0	0	NS
I.V. fluid (ml)	1605 ± 270	1680 ± 380	678 ± 65	< 0.00001
I.V. ephedrine (mg)	0 ± 0	0 ± 0	28 ± 16	< 0.00001
I.V. phenylephrine (mg)	0	0	0	NS

All data are presented as mean ± Standard Deviation. p-value versus EA-F and CSE-F groups.

EA-F : epidural group ; CSE-F : combined spinal epidural group treated with fluids ; CSE-V : combined spinal epidural group treated with vasoconstrictors.

Table 5  
Neonatal Data

	EA-F	CSE-F	CSE-V	p-value
Apgar < 7	2	1	0	NS
pH UA	7.316 ± 0.031	7.264 ± 0.104	7.305 ± 0.054	NS
pH UV	7.337 ± 0.032	7.296 ± 0.103	7.352 ± 0.038	NS
pH UA <7.2	0	1	0	NS
Base Excess	0.83 ± 1.01	-0.50 ± 2.67	-0.95 ± 1.62	NS
Birth weight (g)	1734 ± 991	2485 ± 709	2707 ± 349	< 0.03
NU admission	5	5	2	NS

All data are presented as mean ± Standard Deviation. p-value versus EA-F group.

EA-F : epidural group ; CSE-F : combined spinal epidural group treated with fluids ; CSE-V : combined spinal epidural group treated with vasoconstrictors.

with postdural puncture headache or any other anesthetic complication.

## DISCUSSION

The present trial demonstrates that CSE anesthesia is a safe alternative to conventional epidural anesthesia in severely preeclamptic women. Hypotension did not occur more frequently and was not more pronounced in the CSE groups as compared to the conventional epidural group. This trial also provides evidence that prophylactic ephedrine can safely be used in severe preeclamptic patients without producing excessive hypertension.

Several recent retrospective and prospective studies have shown similar hemodynamic effects of small dose spinal anesthesia compared to epidural anesthesia in preeclamptic patients (3-13, 18). It was also demonstrated that both epidural and spinal anesthesia preserve uteroplacental perfusion in preeclamptic patients (13, 19-21). A recent study by Aya and co-workers even showed a significantly reduced risk of hypotension, almost six times less, in severely preeclamptic patients compared to

healthy patients after spinal anesthesia for cesarean section (14). The present trial adds to the evidence that spinal anesthesia is a safe alternative, even in severely preeclamptic patients, especially when a low dose technique is chosen.

Although the hemodynamic effects of epidural and spinal anesthesia were similar, periods of hypotension occurred in about 50% of our patients, despite prophylactic (fluid or vasopressor) treatment and independent of the regional technique.

In our trial, however, mean arterial pressure remained relatively stable in all three groups and mean reductions in blood pressure were relatively mild. These reductions were less than reported in previous studies (3, 5, 6, 13). HOOD and CURRY (3) reported a decrease of 15-25%, RAMANATHAN *et al.* (6) reported a decrease of about 15% following CSE using 1500 mL crystalloid preloading, whilst WALLACE *et al.* showed a 25% decrease in mean arterial pressure without fluid preloading (5). KARINEN *et al.* found a mean maximum decrease of 19% after 1000 ml preload (13).

In the study of POUTA and coworkers none of the patient's blood pressure decreased more than 20% after 1000 ml crystalloid preloading and another 1000 ml crystalloid after spinal anesthesia (22).

As maternal hypotension can lead to detrimental maternal and neonatal effects, numerous trials studied different strategies in healthy parturients to prevent hypotension but there is no established ideal technique (23). The use of left lateral uterine displacement is routine, IV fluid preloading and the use of prophylactic vasopressors are widely accepted. However prophylactic fluid loading is often disappointing and several studies in healthy obstetric patients do not support the prophylactic use of ephedrine (24).

When vasopressors are used, intravenous ephedrine is the gold standard for prevention of spinal hypotension (25). However, recent literature questions the use of prophylactic ephedrine. The use of ephedrine, especially when higher doses are used, is related to lower umbilical artery pH and a higher incidence of fetal acidosis, probably because of ephedrine-induced  $\beta$ -adrenergic stimulation of the fetus (26-29). Some investigators showed that the use of phenylephrine combined with ephedrine is more likely to be effective and produces less umbilical artery acidosis, with better Apgar scores than ephedrine alone (26-30). To our knowledge the use of ephedrine combined with phenylephrine has not been studied in patients with severe preeclampsia. In the present study, fetal acidosis (defined as umbilical artery pH less than 7.2) occurred in one neonate from the CSE-F group, whilst no fetal acidosis occurred in the EA-F or the CSE-V groups. No significant differences in Apgar scores between the three groups were noted. Apparently prophylactic ephedrine did not produce fetal and neonatal acidosis under the conditions of the present trial. Phenylephrine was not administered in our study.

The hyperdynamic cardio-vascular state (sympathetic hyperactivity) with a high cardiac index, the increased production of circulating factors with a vasopressor effect and the increased sensitivity of blood vessels to vasopressor drugs in patients with severe preeclampsia may lead to an increased risk for hypertensive crises, when vasopressors are aggressively being administered. The doses of ephedrine administered in our study ( $28 \pm 16$  mg) did not lead to hypertensive crises. Ngen Kee reported an incidence of hypertension after 30 mg of prophylactic ephedrine of 45% in healthy women (31). Based on our results prophylactic ephedrine in doses up to 15 mg seems safe in these high risk pregnancies both for mother and child.

Fluid preloading is widely accepted to prevent spinal anesthesia-induced hypotension and in preeclamptic patients it is important because of the

marked reductions in plasma volume and the widespread vasoconstriction in these patients. We limited the preloading volume to 10 mL/kg because of the risk for iatrogenic pulmonary edema associated with excessive fluid loading in preeclamptic patients. Pregnancy leads to a decreased colloid osmotic pressure, acute crystalloid volume preloading of more than 30 mL/kg can lead to a further decrease with an increased risk of pulmonary edema (32). In our study none of the patients developed pulmonary edema. Acute fluid preloading also stimulates the release of atrial natriuretic peptide (ANP) during cesarean section under spinal anesthesia, which has natriuretic, diuretic and vasodilator effects (33) but Frölich reported that the increased level of ANP does not lead to a decreased blood pressure (34).

Our study suffers from a limited recruited number of patients. Indeed, in the CSE-F group standard deviations are much larger than in the other two groups. This may explain why despite a trend towards more prolonged hypotension in this group and worse umbilical artery pH values, no significant differences were identified. We must therefore be careful in interpreting these data, especially the results of the CSE-F group, as a larger number of recruited patients might have resulted in a significant difference. Prolonged hypotension might occur as a result of our methodology. In the CSE-F group hypotension was initially managed with additional fluid loading. It is very much a probability that the effect of additional fluid loading results in some time-loss as compared to the more immediate effect of vasopressors in the CSE-V group.

Furthermore neonates in the conventional epidural group had a lower birth weight than those infants in the two CSE groups ( $1734 \pm 991$  vs  $2485 \pm 709$  and  $2707 \pm 349$  gram). Since intrauterine growth restriction is a hallmark of severe preeclampsia, patients in this group might have been more severely affected than those in the two CSE groups. However, blood pressure, blood work results and proteinuria were not significantly different among the groups.

In conclusion, this prospective randomized study showed that, as in healthy patients, combined spinal and epidural anesthesia (CSE) is a safe alternative to conventional epidural anesthesia in severe preeclamptic women and that the prophylactic use of ephedrine is effective and safe to prevent and treat spinal hypotension after combined spinal and epidural anesthesia for cesarean section in severe preeclamptic women. Larger studies are necessary

to further investigate the safest and most effective management of spinal hypotension in severe preeclamptic patients scheduled for cesarean section under CSE anesthesia. Caution must be used in interpreting the results of this trial since only a limited number of patients were included in this trials. We however hope the results of this trial add to the body of evidence that spinal anesthesia is indeed a safe and valuable option for anesthesia in severe preeclampsia.

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