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Strong ion and weak acid analysis in severe preeclampsia: potential clinical significance†

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Abstract

Background: The influence of common disturbances seen in preeclampsia, such as changes in strong ions and weak acids (particularly albumin) on acid-base status, has not been fully elucidated. The aims of this study were to provide a comprehensive acid-base analysis in severe preeclampsia and to identify potential new biological predictors of disease severity.
Methods: Fifty women with severe preeclampsia, 25 healthy non-pregnant- and 46 healthy pregnant controls (26–40 weeks′ gestation), were enrolled in this prospective case-control study. Acid-base analysis was performed by applying the physicochemical approach of Stewart and Gilfix.
Results: Mean [SD] base excess was similar in preeclamptic- and healthy pregnant women (−3.3 [2.3], and −2.8 [1.5] mEq/L respectively). In preeclampsia, there were greater offsetting contributions to the base excess, in the form of hyperchloraemia ($BE_{(Cl)}$ −2 [2.3] *vs* −0.4 [2.3] mEq/L, $P<0.001$) and hypoalbuminaemia ($BE_{(Alb)}$ 3.6 [1] *vs* 2.1 [0.8] mEq/L, $P<0.001$). In preeclampsia, hypoalbuminaemic metabolic alkalosis was associated with a non-reassuring/abnormal fetal heart tracing ($P<0.001$). Quantitative analysis in healthy pregnancy revealed respiratory and hypoalbuminaemic alkalosis that was metabolically offset by acidosis, secondary to unmeasured anions and dilution.
Conclusions: While the overall base excess in severe preeclampsia is similar to that in healthy pregnancy, preeclampsia is associated with a greater imbalance offsetting hypoalbuminaemic alkalosis and hyperchloraemic acidosis. Rather than the absolute value of base excess, the magnitude of these opposing contributors may be a better indicator of the severity of this disease. Hypoalbuminaemic alkalosis may also be a predictor of fetal compromise.
Clinical trial registration: clinicaltrials.gov: NCT 02164370.

Key words: acid-base balance; pre-eclampsia; pregnancy

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Editor's Key points

- Preeclampsia remains a challenging condition to manage to achieve best fetal and maternal outcomes.
- Defined biochemical changes that could be used to guide management would have clinical utility.
- This study explores using changes in acid-base status as a predictive biomarker of disease severity.
- Preeclamptic, and healthy women had similar base excess but greater hypoalbuminaemic alkalosis and hyperchloraemic acidosis.
- This preliminary work needs to be confirmed in a larger study.

Introduction

Preeclampsia is a major cause of maternal mortality worldwide[1] and is characterized by multi-organ involvement leading to acute and long-term morbidity of mother and newborn.[2 3] In early onset preeclampsia (<34 weeks gestation), expectant management is usually attempted, and fetal lung maturation with a course of 48 h steroids is standard of care.[4] To date, there are few specific biochemical predictors of disease severity, or criteria to guide clinicians in their decision to offer expectant management *vs* prompt delivery. Management is mostly guided by expert opinion-based guidelines.[5]

In other clinical arenas, acid/base measures have been powerful tools in predicting outcomes.[6–8] However, studies evaluating acid-base imbalances in preeclamptic women are scarce, and to our knowledge no comprehensive analysis of independent factors determining acid/base status has been performed. In a previous study, Dyer and colleagues[9] found a mean arterial base excess (BE) of −6.6 [2.8] mEq/L in preeclamptic women undergoing urgent Caesarean delivery for a non-reassuring fetal heart trace, which is greater than the base excess described in healthy pregnancy. This might indicate maternal abnormalities of acid-base status in preeclampsia. As in previous investigations on acid-base status in preeclampsia, these authors focused mainly on describing plasma pH, HCO_3, base excess (BE) or the anion gap (AG).[10–12] Although sufficient to simply describe an alteration in acid/base status in uncomplicated patients, in critically ill patients simultaneous acid/base derangements may offset each other and ultimately lead to a minimally deranged pH, HCO_3, BE and AG.[13–16] Thus conventional analysis may overlook important and informative pathologic processes. A quantitative physicochemical approach analyses the difference in strong plasma cations and anions, the concentration of weak acids (mainly albumin and phosphate), and the P_{CO_2}.[17–19] By applying this approach, multiple severe acid-base disorders have been demonstrated in various disease processes, despite normal pH and BE.[13–15 20 21] As changes in albumin, volume status, and sodium or chloride homeostasis are common in preeclampsia,[1] we hypothesized that they significantly alter acid-base status, but may go unrecognized because of offsetting effects. Therefore, the primary aim of this study was to analyse acid/base balance in women with severe preeclampsia, by applying the physicochemical methods of Stewart[17] and Gilfix.[19] The secondary aim was to identify potential biological predictors for adverse maternal and neonatal outcomes.

Methods

After approval by two institutional Human Research Ethics Committees, and written informed consent, women diagnosed with severe preeclampsia were enrolled in this prospective case control study. The investigation was conducted at the University of Cape Town (UCT), Cape Town, South Africa, [SA, (#IRB 698/2013)], in collaboration with the University of Washington, Seattle, USA, (#IRB 43603, clinicaltrials.gov: NCT 02164370) in accordance with the Declaration of Helsinki and Good Clinical Practice. This observational study was reported using the STROBE guidelines.[22]

Subjects

Preeclampsia group

Women diagnosed with severe preeclampsia, admitted to the Maternity Centres of UCT, were screened for possible enrolment by one of two study investigators (C.O., B.C.) not providing clinical care. Preeclampsia was defined according to the recommendations of the American College of Obstetricians and Gynaecologists[4] and regarded as severe if the systolic blood pressure exceeded 160 mm Hg and/or the diastolic blood pressure exceeded 110 mm Hg on at least two separate occasions, if symptoms of imminent eclampsia were present, or if proteinuria on urine dipstick was 3+ or more. Early onset disease was defined as diagnosis before 34−, and late onset disease after 34 weeks of gestation.

After informed consent, a blood specimen was drawn at the time of diagnosis, as soon as possible after admission. Blood draws were repeated before delivery in women diagnosed with early onset disease. A second blood sample was obtained at the time of the decision to start induction of labour or to undergo Caesarean delivery, if this was more than 24 h after the initial blood sample was obtained.

Recent evidence showing good correlation between arterial and venous metabolic acid-base status,[23 24] prompted the local institutional review board to request a pilot study of 25 paired arterial and venous blood samples to be analysed. This revealed a mean [SD] venous-arterial difference in pH, P_{CO_2}, P_{O_2}, HCO_3^-, BE and SBE of, respectively, −0.00 [0.01], 0.2 kPa [0.19], −6.0 kPa [3.1], 0.6 mmol/l [0.7], 0.4 mEq/L [0.4], and 0.5 mEq/L [0.7], and yielded a statistically significant difference only in P_{O_2}. Therefore, and in order to reduce parturients' discomfort, it was decided to use venous blood gas data for the analysis.

Antenatal management was according to the established protocol of the local institutions at UCT. At the time of diagnosis of severe preeclampsia, seizure prophylaxis was administered, consisting of magnesium sulphate administered as a loading dose of 4 g i.v., followed by 1 g/h i.v. Magnesium sulphate dissolved in 0.9% normal saline and administered at a rate of 50 ml/h, after the loading dose in a 200 ml bolus. Preeclamptic women were otherwise fluid restricted. Blood pressure was managed according to a standardized protocol, using alpha-methyldopa, nifedipine or dihydralazine, and fetal cardiotocography (CTG) was interpreted according to the guidelines of the Royal College of Obstetricians and Gynaecologists.[25] One non-reassuring (early or variable decelerations, fetal basal heart rate 100–119 or 160–179 beats min^{-1} , or variability less than 5 beats min^{-1} for up to 40 min) and 2 normal/reassuring features on CTG defined category II fetal heart tracing. Two or more non-reassuring features or 1 or more abnormal features on CTG (late or prolonged [>3 min] deceleration, fetal basal heart rate <100 or >180 beats min^{-1}, or variability less than 5 beats min^{-1} for greater than 90 min) defined a category III fetal heart tracing, and was considered to be an indication for Caesarean delivery. The decision to proceed with Caesarean delivery was made by the obstetrics team, independent of the investigators.