**2022 Study Protocol**

# Point-of-care ultrasound abnormalities in eclampsia - prevalence and association between pulmonary interstitial syndrome and cardiac dysfunction, brain natriuretic peptide, and serum albumin

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## I. Introduction

Preeclampsia is a life-threatening hypertensive disorder involving the heart and vasculature affecting 5-8% of pregnancies[1]. Untreated, 2-10% of women develop eclampsia[2], defined as new onset of seizures in the setting of preeclampsia[3]. Eclamptic seizures are estimated to occur in 2-8 per 10.000 deliveries in high-income countries (HIC) and with a higher prevalence of up to 16-69 per 10.000 deliveries in low-income countries (LIC)[4,5]. Eclampsia is associated with significant maternal and neonatal morbidity, with a case fatality rate as high as 25-50 % in LIC[2,6], and associated with a 16-26 fold odds of death in HIC[4,5]. Associated maternal complications include intracranial hemorrhage (ICH), cerebral edema, acute kidney injury, acute respiratory syndrome (ARDS), cardiac failure, coagulopathy and postpartum hemorrhage[4]. Obstetric and medical management include seizure prophylaxis and control, aggressive blood pressure management and the urgent delivery of the baby[3]. Anesthesia management can be challenging and has to be tailored to the clinical condition of the eclamptic woman. Unless the usual contraindications to regional anesthesia (RA) apply, spinal anesthesia (SPA) has been described as the method of choice in parturients in whom the Glasgow Coma Scale (GCS) is ≥ 14, and cardiac failure is absent. For patients with persistent decreased level of consciousness, general anesthesia (GA) is recommended.[7] However, in eclamptic women both anesthesia techniques may be associated with significant complications. Raised intracranial pressure (ICP) present in eclamptic women raises the possibility of cerebellar tonsillar herniation in association with SPA. Cardiac diastolic dysfunction, with or without preserved ejection fraction, has been described in preeclamptic women. With preserved ejection fraction, induction of RA or GA is generally hemodynamically well tolerated. However, in women with decreased systolic function, induction of anesthesia can lead to life-threatening cardiovascular collapse, which may only be prevented by cautious titration of anesthesia agents. This might be in conflict with the need to administer high dosages of induction agents to blunt the hypertensive response to tracheal intubation that, if untreated, may lead to life-threatening ICH and pulmonary edema. Consequently, early detection of increased ICP and knowledge of cardiopulmonary function in the individual case are essential to the obstetric anesthetist to guide appropriate management.

Cardiopulmonary and optic nerve sheath point-of-care ultrasound (POCUS) protocols might be particularly suitable for this purpose.[8,9] These involve a defined bedside ultrasound examination to identify critical cardiopulmonary pathophysiology, which may remain undetected by clinical examination alone[8,10,11]. The identification of increased optic nerve sheath diameter (ONSD) on ultrasound may suggest raised ICP[12].
It is further well documented that the serum brain natriuretic peptide (BNP) level, a marker of cardiac dysfunction, is increased in preeclampsia[13,14]. However, no data is available to confirm that elevated BNP levels identify those eclamptic women at risk for cardiopulmonary abnormalities[15].

Therefore, this study is planned to describe the prevalence and severity of cardiac, lung and ONS US abnormalities in women with eclampsia. In a recent study on POCUS findings in late onset preeclampsia, the absence of pulmonary interstitial syndrome (PIS) may exclude raised LVEDP[16]. The **primary aim** of the current study is to examine the association between PIS, as identified by lung ultrasound, and cardiac dysfunction on echocardiography, in eclamptic women. The **secondary aims** are the performance of a comprehensive cardiac ultrasound assessment including a strain analysis, and to explore the association between PIS and ONSD, serum BNP and albumin.

## II. Methods

In this prospective cohort study, preeclamptic women presenting with new onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction or intracranial hemorrhage arising from non-obstetric pathology, or drug use, will be enrolled. Preeclampsia will be defined according to the recommendations of the American College of Obstetricians and Gynecologists (Table 1)[17]. Early onset disease will be defined as diagnosis before 34 weeks of gestation, and late onset disease as after 34 weeks. Given the high prevalence of the disease and the presence of established detailed management protocols, data collection will be performed in the Maternity Centre at Groote Schuur Hospital at the University of Cape Town, Cape Town, South Africa.

Table 1: ACOG diagnostic criteria for preeclampsia

| | |
|---|---|
| **Blood Pressure** | • > 140 mmHg systolic ± 90 mmHg diastolic after 20 weeks gestation<br>• (Severe: > 160 mmHg systolic ± 110 mmHg diastolic) |
| & | |
| **Proteinuria** | • 300 mg in 24h or<br>• Prot./Creat. ratio > 0.3 or<br>• > 1+ dipstick |
| **OR** in absence of proteinuria, new onset hypertension AND presence of ≥ 1 severity feature: | |
| **Thrombocytopenia** | • <100 x $10^9$ / L |
| **Renal insufficiency** | • serum creatinine >1.1 mg/dl or x 2 |
| **Impaired liver function** | • 2 x LFTs |
| **Pulmonary edema** | |
| **Cerebral or visual symptoms** | |

### ***A) Patient screening, enrolment, inclusion, non-inclusion and consent***

On a daily basis, the obstetrics consultant and/or senior registrar in charge will inform the anaesthesia member of the research team should a patient be eligible for the study and her clinical condition allow recruitment and conduction of the ultrasound protocol.

The patient will be approached after completion of normal obstetric treatment protocols, and asked for permission to study their medical file for research purposes. After screening

for inclusion and non-inclusion criteria, the patient will be enrolled and written consent obtained. For details of the consent process, please see III. Ethics Considerations, pages 16-17.

***B) Inclusion / Non-inclusion criteria***

Inclusion criteria are diagnosis of preeclampsia following ACOG definition (Table 1) with new onset of tonic-clonic seizures. Non-inclusion criteria are chronic pulmonary disease, collagen disorders, HIV infection, chronic renal or hepatic disease, urinary tract infection, sepsis, and body mass index (BMI) > 50 $kg/m^2$, history of seizure disorder, intracranial hemorrhage, or history of benign or malignant intracranial neoplasia.

***C) Exclusion criteria***

Following consent and inclusion in the study, women either withdrawing consent, or not giving retrospective consent, will be excluded.

***D) Time point of ultrasound examination***

Maternal ultrasound examinations will be performed after normal obstetric treatment protocols have been completed, i.e., the conduction of the study will contribute no delay in routine or emergency patient management. Ultrasound examination will be repeated after 72-96 hours, subject to the same conditions.

***E) Ultrasound procedures***

An ultrasound examination (approximately 35-40 minutes in duration) will be performed, at which time a venous blood sample will be taken. In addition to venepuncture for measurement of BNP, an additional 2 x 5 ml samples (in vacutainer serum separation collection tubes) will be taken for storage (-80$^{o}$C) and subsequent batch serum measurement of sFlt-1, PlGF and Kisspeptin as surrogate biomarkers for placental dysfunction. The ultrasound examination will consist of evaluation of lung- and cardiac ultrasound, as well as optic nerve sheath diameter.

*Ea) Cardiac Ultrasound:*

*Eaa) 2D echocardiography*

The cardiac ultrasound examination will be performed using a GE Vivid Q® ultrasound machine equipped with a 3.5-MHz transducer. Images will be acquired at rest in the left lateral decubitus position from standard parasternal and apical views. Digital loops of 3 cardiac cycles with associated electrocardiogram information will be stored on the hard disk of the ultrasound machine and transferred to a GE EchoPac® work-station for offline analysis. Analysis will be performed according to existing guidelines.[18-20] Ventricular wall and chamber dimensions will be measured in the parasternal long axis view. Left atrial volume (LAV) and left ventricular volume in diastole (LVEDV) will be calculated from apical views. Right atrial area, right ventricular basal and mid cavity diameter and right ventricular longitudinal diameter will be measured from apical views. Proximal and distal right ventricular outflow tract (prox. and dist. RVOT) will be measured in parasternal short axis views. Tricuspid annular plane systolic excursion (TAPSE) will be measured from apical M-Mode images. Right ventricular fractional area change will be calculated from apical views. Doppler images will be used to measure early and late mitral and tricuspid valve inflow velocities (E and A, RV E and RV A), mitral and tricuspid inflow deceleration time (DT, RV DT), isovolumetric relaxation time (IVRT), systolic and diastolic flow in the pulmonary veins, duration of the late mitral valve inflow (A dur), duration of the flow in the pulmonary vein during atrial contraction (AR dur) and acceleration time of the flow through the pulmonary valve (PV acc. time). Tissue Doppler images will be used to measure systolic (S'), early diastolic (E') and late diastolic (A') tissue velocities at the septal and lateral mitral valve and at the right ventricular free wall. Left ventricular mass will be calculated using the Devereux formula $0.8(1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]) + 0.6$, where LVEDD is left ventricular end diastolic diameter, IVSd is thickness of the interventricular septum in diastole and PWd is posterior wall thickness in diastole. Relative wall thickness will be calculated using the formula (2*PWd)/LVEDD. Total vascular resistance (TVR) will be calculated using the formula 80*MAP/(CO/1000), where MAP is mean arterial pressure and CO cardiac output. Diastolic dysfunction will be classified according to the guidelines of the American Society of Echocardiography and European Society of Cardiovascular Imaging, applying the age and gender adapted values from the 2016 Guidelines.[21]

*Eab) Speckle tracking echocardiography*

The myocardium will be traced manually and EchoPac® software used to identify the area of interest, by delimiting the endocardium and epicardium. The operator will readjust this area before the software will calculate deformation. LV and RV global longitudinal strain and strain rate will be calculated from apical views, with negative values indicating fiber shortening. LV rotation and de-rotation will be calculated from apical and basal parasternal short axis views, with negative values indicating rotation in the clockwise direction. LV twist is the difference between the apical and the basal rotation, LV torsion is LV twist divided by left ventricular length in diastole. If >1 segment is rejected, subjects will be excluded from statistical analysis.

Eb) Lung Ultrasound

Lung ultrasound will be performed with the patient in the supine position. A phased-array transducer will be used for lung ultrasound, and will be used for the assessment of B-lines, which arise from the pleural line and extend to the bottom of the screen, and move with the sliding lung (Figure 1[22]). We will quantify the B-line burden in lung regions using the validated eight-region method[23], as previously described: Two anterior and two lateral regions in each hemithorax will be evaluated. If 3 or more B-lines (any size and spaced apart by any distance) are present in a particular region, that region is considered positive. Two or more positive regions per side define a "B-line pattern."

Ec) Ultrasound of optic nerve sheath (ONS)

Measurement of optic nerve sheath diameter will be performed applying the coronal technique[24] with a linear transducer placed in a vertical (cephalad-caudal) orientation at the lateral canthus and aimed nasally and posteriorly until a circular optic nerve is seen at its largest diameter. Measurements will be taken in a superior-inferior direction to minimize artifact if the image is taken at a slightly oblique angle (Figure 2[24]).The patient will be positioned supine (with or without left uterine displacement, depending on clinical circumstances), with a 30 degree head elevation. After the point of entry of the optic nerve into the globe has been identified, the image will be frozen. Optic nerve sheath diameter

will be measured 3 mm behind the globe in a perpendicular axis to the nerve (Figure 3[25]). Two measurements will be taken per eye, and the mean of the 4 values will represent the optic nerve sheath diameter.

*F) Statistical analysis*

Data will be presented as mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. For the a priori defined ultrasound outcomes of PIS, diastolic dysfunction, and increased ONSD, the prevalence and 95% confidence intervals will be calculated. In addition, the prevalence and 95% confidence intervals of systolic dysfunction and of raised LVEDP will be calculated.

Patients with and without ultrasound abnormalities will be compared with respect to admission systolic and diastolic blood pressures, clinical features of disease severity, and mean BNP levels using 2-sample t-test and the Chi-square test, for continuous and categorical variables respectively. The associations between PIS, increased ONSD or diastolic dysfunction with clinical severity features (=high arterial blood pressures, presence of pulmonary edema, headaches or visual disturbances, raised liver or renal laboratory parameters tests, and low platelet count), serum albumin level, BNP level, and between cardiac and pulmonary ultrasound abnormalities, will be explored using the 2-sample t-test and the Chi-square test, for categorical and continuous variables respectively. To adjust for multiple comparisons, including primary and secondary outcomes, a Benjamini-Hochberg correction will be applied using a 10% false discovery rate. Assuming that the p-value will result from 32 direct comparisons made in the study, the significance level will be adjusted to $p < 0.025$.

In order to determine pre- and post-test probabilities of PIS to predict elevated LVEDP, and of BNP at a level above 200 pg/ml to predict systolic dysfunction, diastolic dysfunction, elevated LVEDP, and the presence of PIS, sensitivity, specificity, positive and negative predictive value will be calculated.

Intra- and inter-observer agreement will evaluated using the Bland and Altman method, after reviewing 10% of lung- (using total B-line score), cardiac- (using left ventricular internal diameter in diastole (LVEDD), and optic nerve (using the left optic nerve sheath

diameter) parameters; results will be expressed both graphically and quantitatively as mean difference (bias) and 95% limits of agreement.

*Sample size calculation*

The sample size calculation is based upon the primary aim, which is to examine the association between PIS on lung ultrasound and raised LVEDP on cardiac ultrasound. Available data on women with late onset preeclampsia and severe features suggest that the incidences of PIS and raised LVEDP are 23/95 (24%; 95% CI: 16-34%), and 20/80 (25%; 95% CI: 16-36%) respectively.[16] In that population, the proportion of women with raised LVEDP was 12% in patients without PIS, and 55% in those who had PIS. A sample size of 60 (45 LVEDP negative and 15 LVEDP positive) will be required to detect a significant difference in incidence of PIS between the 2 groups (52% [expected PIS positive rate in women with raised LVEDP] versus 15% [expected PIS positive rate in women with normal LVEDP]) with a power of 80% and significance level of 0.05. To allow for the possibility of poor image acquisition during positive pressure ventilation, 70 patients will be recruited.

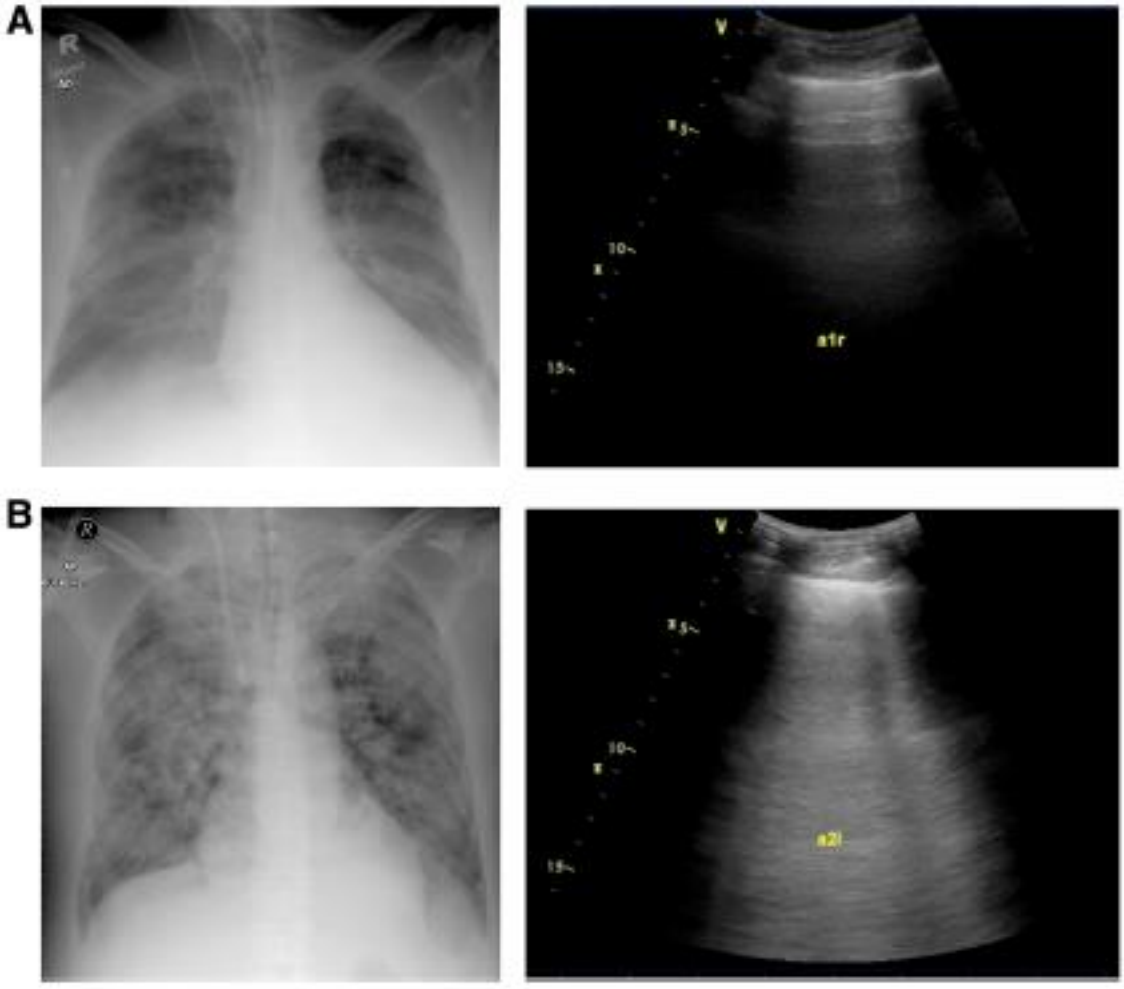


Figure 1: Comparison of normal lung in Panel A versus B-line pattern in Panel B[22].

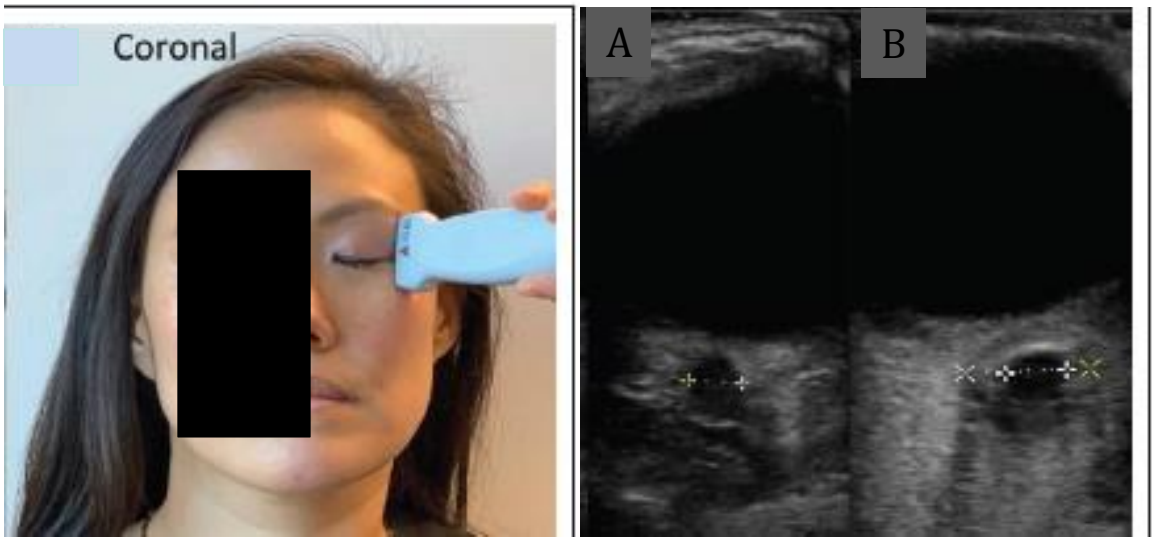


Figure 2 (Image from Ref.[24]): Measurement of the optic nerve sheath diameter in the coronal axis. The view is obtained in a sharply demarcated circle, measured in its widest diameter (A). If edema is seen, the measurement is taken at the outer edge (B, outer calipers).[24]

## III. Ethics considerations

### A. Risks and benefits

There is very little risk to subjects participating in this study. If possible, venous blood samples will be taken as part of routine sampling performed in patients diagnosed with eclampsia. If not possible, a maximum of one venipuncture (1-2 ml) will be required in addition to routine blood sampling. In all cases, the blood samples will be taken and examinations performed as soon possible after admission, always allowing for prior initiation of normal obstetrics treatment protocols. Expected duration of blood sampling and ultrasound examinations is 30-45 minutes. In the event of demonstration of decreased systolic function (ejection fraction < 40%) and/or valvular heart disease, the obstetrics and anesthesia management team would be informed, since such findings could influence further management.

### B. Informed Consent

Details of the consent process and data inclusion in the study are as follows:

1 Patients with eclampsia who are scheduled for induction of labour will have adequate cognition and the capacity for informed consent before the onset of labour. Patients will be given the consent form and given sufficient time to read it and ask questions. The discussion will be presented in an open, non-intimidating and educational format, in the patient's preferred language. All attempts will be made to minimise any anxiety that our study procedure may provoke; we will continually communicate with the patient regarding what to expect and explain that the investigations are noninvasive.

2 Patients who are scheduled for urgent caesarean section for maternal and/or fetal indications, will not have the capacity for informed consent at this time. In these cases, we will only be able to explain the study to the patient after clinical improvement from the post-anaesthesia state, and/or clinical improvement of their condition. Should the patient receive spinal anaesthesia, or be extubated immediately post-general anaesthesia, consent will proceed as in 1, above, as soon as there is full recovery from anaesthesia, and the patient has capacity.

3 In patients who require postoperative ventilation and who are haemodynamically stable, in order to avoid the risk of futility (since the important pathophysiological changes could be missed by delaying the noninvasive ultrasound protocol), the research group asks for an initial waiver of consent. We respectfully request that the family will not be contacted at this point, in the interest of allaying their anxiety in a stressful situation. The researchers therefore request "delayed consent", which can be given by the patient (following stabilisation or recovery), or next of kin, or a legal representative or proxy. If the patient refuses consent, the data will not be used.

4 In view of recent work showing that in South Africa teenage mothers are at highest risk of eclampsia (Nathan et al, Journal of Global Health 2018:8: 020401), we request that minors (patients under the age of 18 years) may also be recruited for these noninvasive ultrasound scans. In these circumstances, parental approval will be requested, together with assent by the patient. The same initial waiver is respectfully requested for a patient requiring mechanical ventilation, as in 3, above. "Delayed consent" would then involve requesting parental approval and the assent of the patient after recovery. Should it be impossible to make contact with the parents, the research group will contact the HREC for a decision in the individual case.

4 In the unusual event of a diagnosis of intracerebral haemorrhage or stroke, the patient will be excluded from the study. In the rare event of the demise of a patient for any reason other than intracerebral haemorrhage or stroke, the researchers request that the data be included and analysed, after discussion with the HREC, for the reasons below.

The justifications for the above consent process and data inclusion are the following: Exclusion of patients without the capacity for consent, including minors, would lead to a biased sample, and data which is not generalisable to the majority of women with eclampsia. The generation of biased and poorly generalisable data would not address the research question and would thus dishonour the contributions of the other included patients, and would be wasteful research in a resource-limited environment.

C. Steps during the recruitment process to minimize potential coercion and anxiety

Patients will be assured that confidentiality will be guaranteed concerning any stored data, and that participation or non-participation in the study will not influence their quality of

care. Any patient anxiety will be allayed by sensitive discussion during the consent process; patients will be assured that the risks of ultrasound examination are minimal, and that the procedure is completely noninvasive. Patients will also be assured that they can withdraw from the study at any point.

D. Data Management

The study data will be coded, and we will maintain identifiers separate from the coded study data. The link between subject medical record number (MRN) and study code number will be kept in a locked office in a locked file, separate from data collected during the course of the study.

Only members of the research team will have access to the data until final collection and analysis is complete. Once the data is input into a database the data will be identified by study code number. The link to patient identity will similarly be kept in a password protected file in a locked office until the links are finally deleted. Information from the research study will NOT be placed in the patients' medical record. Ultrasound recordings will be saved on ultrasound machine de-identified under the study code number. Identifiers will be kept until 7 years of completion of enrollment to ensure accuracy of data collection during analysis.

**References**


1. Leffert LR. What's new in obstetric anesthesia? Focus on preeclampsia. Int J Obstet Anesth 2015;24:264-71.
2. Goldenberg RL, Jones B, Griffin JB, et al. Reducing maternal mortality from preeclampsia and eclampsia in low-resource countries--what should work? Acta Obstet Gynecol Scand 2015;94:148-55.
3. Sutton ALM, Harper LM, Tita ATN. Hypertensive Disorders in Pregnancy. Obstet Gynecol Clin North Am 2018;45:333-47.
4. Liu S, Joseph KS, Liston RM, et al. Incidence, risk factors, and associated complications of eclampsia. Obstet Gynecol 2011;118:987-94.
5. Fong A, Chau CT, Pan D, Ogunyemi DA. Clinical morbidities, trends, and demographics of eclampsia: a population-based study. Am J Obstet Gynecol 2013;209:229 e1-7.
6. O'Connor HD, Hehir MP, Kent EM, et al. Eclampsia: trends in incidence and outcomes over 30 years. Am J Perinatol 2013;30:661-4.
7. Hofmeyr R, Matjila M, Dyer R. Preeclampsia in 2017: Obstetric and Anaesthesia Management. Best Pract Res Clin Anaesthesiol 2017;31:125-38.
8. Barber RL, Fletcher SN. A review of echocardiography in anaesthetic and peri-operative practice. Part 1: impact and utility. Anaesthesia 2014;69:764-76.
9. Holm JH, Frederiksen CA, Juhl-Olsen P, Sloth E. Perioperative use of focus assessed transthoracic echocardiography (FATE). Anesth Analg 2012;115:1029-32.
10. Fagley RE, Haney MF, Beraud AS, et al. Critical Care Basic Ultrasound Learning Goals for American Anesthesiology Critical Care Trainees: Recommendations from an Expert Group. Anesth Analg 2015;120:1041-53.
11. Lichtenstein D. Lung ultrasound in the critically ill. Curr Opin Crit Care 2014;20:315-22.
12. Amini A, Kariman H, Arhami Dolatabadi A, et al. Use of the sonographic diameter of optic nerve sheath to estimate intracranial pressure. Am J Emerg Med 2013;31:236-9.
13. Rafik Hamad R, Larsson A, Pernow J, Bremme K, Eriksson MJ. Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. J Hypertens 2009;27:2257-64.
14. Fayers S, Moodley J, Naidoo DP. Cardiovascular haemodynamics in pre-eclampsia using brain naturetic peptide and tissue Doppler studies. Cardiovasc J Afr 2013;24:130-6.
15. Afshani N, Moustaqim-Barrette A, Biccard BM, Rodseth RN, Dyer RA. Utility of B-type natriuretic peptides in preeclampsia: a systematic review. Int J Obstet Anesth 2013;22:96-103.
16. Ortner CM, Krishnamoorthy V, Neethling E, et al. Point-of-Care Ultrasound Abnormalities in Late-Onset Severe Preeclampsia: Prevalence and Association With Serum Albumin and Brain Natriuretic Peptide. Anesth Analg 2019; 28: 1208-16.
17. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2019;133:e1-e25.
18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society

of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39 e14.
19. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32:1-64.
20. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
21. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60.
22. Enghard P, Rademacher S, Nee J, et al. Simplified lung ultrasound protocol shows excellent prediction of extravascular lung water in ventilated intensive care patients. Crit Care 2015;19:36.
23. Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38:577-91.
24. Agrawal A, Cheng R, Tang J, Madhok DY. Comparison of Two Techniques to Measure Optic Nerve Sheath Diameter in Patients at Risk for Increased Intracranial Pressure. Crit Care Med 2019.
25. Dubost C, Le Gouez A, Jouffroy V, et al. Optic nerve sheath diameter used as ultrasonographic assessment of the incidence of raised intracranial pressure in preeclampsia: a pilot study. Anesthesiology 2012;116:1066-71.

## IV. **Appendix:**

Maternal and Neonatal data collection and definition of adverse perinatal outcome:

A) Neonatal variables preterm:

- Cardiotocogram (CTG): reactive, non-reactive, abnormal
- normogram estimated fetal weight (intrauterine growth restriction)
- placental abruption,
- fetal distress requiring cesarean section

B) Neonatal post-delivery variables:

- Neonatal birth weight,
- APGAR scores at 1 and 5 minutes
- perinatal death
- admission to neonatal ICU

C) Ultrasound data:

-optic nerve sheath diameter

-B-line score

-diastolic Doppler parameters

D) Maternal demographic data:

- patient age,
- BMI, parity,
- gestational age at diagnosis of severe disease
- past medical history
- smoking status

E) Maternal clinical data:

- blood pressure
- proteinuria
- urine output
- presence of headache or visual disturbances
- oxygen saturation

- presence of abdominal pain
- liver function
- coagulation status
- need for C-section
- indication for C-section