Jana Ambrožič

ULTRASONOGRAPHIC ASSESSMENT OF HEMODYNAMIC CHANGES AND CARDIAC FUNCTION IN PATIENTS WITH SEVERE FEATURES OF PREECLAMPSIA

DOCTORAL DISSERTATION

ULTRAZVOČNA OCENA HEMODINAMIČNEGA STANJA IN SRČNE FUNKCIJE PRI TEŽKI PREEKLAMPSIJI

DOKTORSKO DELO

Ljubljana, 2018
Jana Ambrožič

ULTRASONOGRAPHIC ASSESSMENT OF HEMODYNAMIC CHANGES AND CARDIAC FUNCTION IN PATIENTS WITH SEVERE FEATURES OF PREECLAMPSIA

ULTRAZVOČNA OCENA HEMODINAMIČNEGA STANJA IN SRČNE FUNKCIJE PRI TEŽKI PREEKLAMPSIJI

Mentor and co-mentor appointed by the Academic Senate on 12th September 2017
Examination Committee appointed by the Academic Senate on 10th April 2017
Defense date:

Mentor: Assist. Prof. Miha Lučovnik, MD, PhD
Co-mentor: Assist. Prof. Katja Prokšelj, MD, PhD
Examination Committee Chair: Assist. Prof. Borut Jug, MD, PhD
Examination Committee Member: Prof. Tatjana Stopar Pintarič, MD, PhD
Examination Committee Member: Assist. Prof. Manfred Georg Mörtl, MD, PhD
ACKNOWLEDGMENT

I would like to express my very great appreciation to my main mentor Assist. Prof. Miha Lučovnik, MD, PhD who gave me the opportunity to do this research project and offered me extensive support and encouragement throughout my work. We first met many years ago when we both worked at the emergency department. After several years our professional paths crossed again. He challenged me with cardiology issues in an obstetric population. It was he who initiated the idea to integrate knowledge across different fields of expertise, which resulted in this work that tries to explore complex hemodynamic maternal changes before and early after delivery focusing on cardiological aspects.

Many thanks also to my co-mentor Assist. Prof. Katja Prokšelj, MD, PhD for her valuable contribution and giving this work an additional pair of eyes thus helping this paper assume its final form.

Furthermore, I would like to acknowledge the crucial role of all of the staff members of the Department of Perinatology at University Medical Center Ljubljana, with the former head Assist. Prof. Nataša Tul Mandić, MD, PhD in enabling me to perform this study. I would like to express my special thanks to all the women for their willingness to participate in the research.

I owe a special gratitude to my cardiology colleague Marta Cvijić, MD, PhD for her valuable suggestions and encouraging attitude during the final steps in putting data together. She taught me a lot about the research work so her assistance is greatly appreciated.

Last but not least I would like to thank my family for understanding and support throughout this research and my professional endeavors in general.
# TABLE OF CONTENTS

ACKNOWLEDGMENT 5

TABLE OF CONTENTS 7

ABBREVIATIONS AND ACRONYMS 9

ABSTRACT 13

INTRODUCTION 15

Classification of hypertensive disorders during pregnancy 15

Epidemiology of preeclampsia 17

Pathogenesis of preeclampsia 19

Cardiovascular changes in normal pregnancy 20

Cardiovascular changes in women with preeclampsia 22

Management of preeclampsia with severe features 25

Non-invasive assessment of maternal hemodynamics 26

THE AIM OF THE STUDY 27

HYPOTHESES 28

METHODS 28

Study population 28

Study protocol 29

Ultrasound examination 30

Lung ultrasound 33

Fluid responsiveness 35

Statistical analysis 35

RESULTS 35

Study population characteristics 35

Hemodynamic characteristics 37

Cardiac geometry 39

Napaka! Zaznamek ni definiran.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>peak late diastolic mitral inflow velocity</td>
</tr>
<tr>
<td>APLAX</td>
<td>apical long axis</td>
</tr>
<tr>
<td>AGA</td>
<td>appropriate for gestational age</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>AVC</td>
<td>aortic valve closure</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CI</td>
<td>cardiac index</td>
</tr>
<tr>
<td>CO</td>
<td>cardiac output</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>DT</td>
<td>deceleration time</td>
</tr>
<tr>
<td>E</td>
<td>peak early diastolic mitral inflow velocity</td>
</tr>
<tr>
<td>e′</td>
<td>peak early diastolic myocardial velocity</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ECS</td>
<td>echo comet score</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>GLS</td>
<td>global longitudinal strain</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>INF-LAT</td>
<td>inferolateral wall</td>
</tr>
<tr>
<td>IVS</td>
<td>interventricular septum</td>
</tr>
<tr>
<td>LA</td>
<td>left atrium/atrial</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle/ventricular</td>
</tr>
<tr>
<td>LVEDD</td>
<td>left ventricular internal diameter at end diastole</td>
</tr>
<tr>
<td>LVEDV</td>
<td>left ventricular end-diastolic volume</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>LVESD</td>
<td>left ventricular internal diameter at end systole</td>
</tr>
<tr>
<td>LVESV</td>
<td>left ventricular end-systolic volume</td>
</tr>
<tr>
<td>LVOT</td>
<td>left ventricular outflow tract</td>
</tr>
<tr>
<td>LVOT D</td>
<td>left ventricular outflow diameter</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MAPSE</td>
<td>mitral annular plane systolic excursions</td>
</tr>
<tr>
<td>NPIS</td>
<td>National Perinatal Information System</td>
</tr>
<tr>
<td>PLR</td>
<td>passive leg raising</td>
</tr>
<tr>
<td>PVR</td>
<td>peripheral vascular resistance</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>s’</td>
<td>peak systolic myocardial velocity</td>
</tr>
<tr>
<td>SGA</td>
<td>small for gestational age</td>
</tr>
<tr>
<td>SRe</td>
<td>global early diastolic strain rate</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
<tr>
<td>SW</td>
<td>stroke work</td>
</tr>
<tr>
<td>VTI</td>
<td>left ventricular outflow tract velocity-time integral</td>
</tr>
<tr>
<td>2ch</td>
<td>2-chamber view</td>
</tr>
<tr>
<td>4ch</td>
<td>4-chamber view</td>
</tr>
</tbody>
</table>
ABSTRACT

Objective. The objective of this study was to assess whether echocardiographic parameters in combination with lung ultrasound can detect dynamic changes in hemodynamic status, cardiac function and lung congestion in women with severe features of preeclampsia and healthy controls immediately before and in the first days after delivery. We hypothesized that women with severe features of preeclampsia more frequently present with impaired left ventricular diastolic function, have higher degree of lung congestion that is related to impaired diastolic function parameters and are less fluid responsive compared with healthy pregnant women.

Methods. 30 severe preeclamptic women and 30 healthy term controls were evaluated within 1 day before delivery, 1 day post-delivery and 4 days post-delivery. At each examination standard two-dimensional, pulsed wave and tissue Doppler echocardiography was performed. Left ventricular myocardial deformation parameters were assessed by two-dimensional speckle tracking imaging. Lung ultrasound was performed by the 28-rib interspaces technique and Echo Comet Score (ECS) was obtained as the sum of B-lines representing the amount of extravascular lung water. Fluid responsiveness was assessed by measuring changes in left ventricular stroke volume with passive leg rising and it was defined as an increase in stroke volume of at least 12%.

Results.

Hemodynamic characteristics

Women with severe features of preeclampsia had significantly higher arterial blood pressures (mean arterial pressure: median 110 (range 103 – 119) mmHg vs. 88 (81 – 96) mmHg, p < 0.001) and peripheral vascular resistance (1694 (1480 – 1871) dynes×s×cm⁻5 vs. 1411 (1173 – 1612) dynes×s×cm⁻5, p = 0.004), while heart rate (77 (70 – 89) bpm vs. 75 (69 – 84) bpm, p = 0.736) and stroke volumes (70 (61 – 78) ml vs. 68 (57 – 76) ml, p = 0.194) were comparable between both groups.

Left ventricular systolic and diastolic function

Ejection fraction was similar in both groups at all examinations (before delivery: 66 (64 – 71)% vs. 66 (61 – 67)%, p = 0.061; 1 day post-delivery: 65 (62 – 70)% vs. 64 (62 – 66)%, p = 0.09; 4 days post-delivery: 64 (60 – 71)% vs. 65 (60 – 69)%, p = 0.592);
however, peak systolic myocardial velocities (s’) at the septal and lateral mitral annulus and global longitudinal strain values (GLS) were lower in preeclamptic women 4 days post-delivery (s’ at the septal mitral annulus: 7.4 (6.6 - 7.8) cm/s vs. 8.1 (7.9 - 9.3) cm/s, p = 0.001; GLS: –21.7 (–22.6 to –20.8)% vs. –23.0 (–23.9 to –21.8)%, p = 0.027). At all assessments peak early diastolic myocardial velocities (e’) were significantly lower (e’ at the septal mitral annulus before delivery: 8.7 (7.0 - 10.3) cm/s vs. 9.0 (8.2 - 10.7) cm/s, p = 0.062; 1 day post-delivery: 8.2 (7.2 - 9.6) cm/s vs. 9.8 (8.7 - 11.0) cm/s, p = 0.001; 4 days post-delivery: 8.5 (7.7 - 9.6) cm/s vs. 10.3 (9.0 - 12.1) cm/s, p < 0.001) and the ratio of the peak velocity of early diastolic mitral inflow (E) to e’ (E/e’) was significantly higher in preeclamptic women than in controls (before delivery: 8.2 (6.3 - 10.1) vs. 6.3 (5.3 - 7.7), p = 0.002; 1 day post-delivery: 8.6 (7.6 - 10.2) vs. 6.9 (6.2 - 7.7), p = 0.001; 4 days post-delivery: 8.3 (7.1 - 9.0) vs. 6.8 (5.9 - 7.3), p = 0.003).

**Lung ultrasound and fluid responsiveness**

ECS was significantly higher in preeclamptic women than in controls before delivery (16 (9 – 25) vs. 6 (2 – 7), p < 0.001) and 1 day post-delivery (15 (8 – 26) vs. 9 (6 – 14), p = 0.007), but not 4 days post-delivery (7 (2 – 13) vs. 4 (2 – 8), p = 0.091). Significant positive correlations between ECS and E/e’ were found before and immediately post-delivery in preeclamptic group (Spearman, before delivery: r = 0.572, p = 0.001; 1 day post-delivery: r = 0.442, p = 0.018). Fluid responsiveness was observed in significantly more controls than in women with severe features of preeclampsia (12 (43%) vs. 3 (11%), p = 0.014) before delivery.

**Conclusions.** Preeclampsia with severe features is associated with impaired diastolic function parameters that persist in the first days after delivery. Preeclamptic women have greater amount of extravascular lung water before and immediately post-delivery compared with healthy controls and lung congestion correlates with impaired parameters of diastolic function. Worsening of systolic function parameters 4 days after delivery in preeclamptic women might indicate subtle systolic dysfunction, which could become unmasked with the effect of augmented volume load related to fluid mobilization in the postpartum period. This finding seems to corroborate our results of passive leg raising test showing that the majority of preeclamptic women were fluid non-responsive and as such, could not be able to increase myocardial contraction force with fluid loading.
INTRODUCTION

Classification of hypertensive disorders during pregnancy

Hypertensive disorders of pregnancy include 1) chronic (pre-existent) hypertension; 2) pregnancy induced hypertension, which is further divided into preeclampsia (characterized by new-onset hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation) and gestational hypertension (characterized by new-onset hypertension after 20 weeks of gestation without signs and symptoms of end-organ dysfunction); and 3) chronic hypertension with superimposed preeclampsia \(^1\text{-}^3\). Diagnostic criteria for preeclampsia and preeclampsia with severe features (formerly known as severe preeclampsia) are presented in Tables 1 and 2, respectively \(^1\).
Table 1. Diagnostic criteria for preeclampsia. Adapted from ref. 1.

| Blood pressure | • Greater than or equal to 140 mmHg systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure  
|               | • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mmHg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy  

**And**

| Proteinuria   | • Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection)  
|               | • Protein/albumin ratio greater than or equal to 30 g/mol  
|               | • Dipstick reading of 1+ (used only if other quantitative methods not available)  

**Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:**

| Thrombocytopenia | • Platelet count less than 100x10⁹/L  
| Renal insufficiency | • Serum creatinine concentration greater 97 µmol/L or a doubling of the serum creatinine concentration in the absence of other renal disease  
| Impaired liver function | • Elevated blood concentrations of liver enzymes (to twice normal concentration)  
| Pulmonary edema |  
| Cerebral or visual symptoms | 
Table 2. Diagnostic criteria for preeclampsia with severe features (any of the following). Adapted from ref 1.

- Systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100x10^9/L)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration greater 97 µmol/L or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset cerebral or visual disturbances

Epidemiology of preeclampsia

Preeclampsia complicates 2 to 8% of pregnancies and remains one of the leading causes of maternal as well as perinatal morbidity and mortality worldwide 4,5. It is a complex multiorgan disease potentially involving the kidney, liver, brain and cardiovascular and hematologic systems. Preeclampsia with severe features occurs in approximately 0.5% of pregnancies with an incidence of 0.1 to 2.7% in the different regions 6. Deaths in preeclamptic patients are due to intracranial hemorrhage and cerebral infarction, acute pulmonary edema, hepatic failure or rupture and bleeding such as may occur with disseminated intravascular coagulation or placental abruption.

The incidence of preeclampsia in Slovenia is 2 to 3% (data from the National Perinatal Information System - NPIS). Five of 36 (13.8%) maternal deaths in Slovenia between 2000 and 2014 were due to preeclampsia; and hemorrhagic stroke was the cause of death in all five cases (National Institute for Public Health data) (Figure 1). Moreover, medically indicated preterm birth due to preeclampsia accounts for approximately 10%
of all very preterm births (births at < 32 weeks of gestation when risks for neonatal mortality and severe morbidity are especially high) (NPIS) (Figure 2).

Figure 1. Maternal deaths in Slovenia in 2000-2014, Slovenian Institute for Public Health.
Besides the immediate short-term mortality and morbidity that may occur from the disease during pregnancy, preeclampsia is also associated with long-term risks. Over the past 10 years lots of data has accumulated indicating that a woman who has had a preeclamptic pregnancy is at an increased risk of cardiovascular disease later in life \(^1,7-13\).

**Pathogenesis of preeclampsia**

The etiology and molecular basis of preeclampsia are not fully understood. There is evidence of underlying genetic, immunological and environmental factors \(^14\). Principal pathology lies in the impaired development of placental vasculature resulting in relative placental hypoperfusion and ischemia \(^15,16\). Antiangiogenic factors released from the placenta into maternal circulation provoke generalized maternal endothelial dysfunction and systemic hypertension. Endothelial dysfunction is the basis for the multiple clinical manifestations of the disease. Evidence of genetic predisposition comes from the findings that preeclampsia may run in families \(^17\). Many of the gene variants associated with preeclampsia are also risk factors for developing cardiovascular diseases, suggesting that
pre-existing endothelial damage might be the common principal pathology in women susceptible to developing preeclampsia and cardiovascular disease later in life 18,19. Therefore, it has been proposed that failure of the maternal cardiovascular system to adapt to pregnancy may be the primary mechanism leading to secondary placental dysfunction in preeclampsia 20.

**Cardiovascular changes in normal pregnancy**

During pregnancy the cardiovascular system undergoes a set of physiological changes due to increased metabolic demand of the uteroplacental fetal unit, which requires adequate uteroplacental circulation. There is an increase in blood volume leading to an increase in venous preload. Cardiac output increases due to an earlier increase in stroke volume, followed by an increase in heart rate later during gestation (Figure 3). On the other side, there is a decrease in peripheral vascular resistance leading to a decrease in left ventricular (LV) afterload 21. Correspondingly, there is initial decrease in systemic blood pressure, which reaches its lowest value at mid-pregnancy and begins to increase again in the last trimester to pre-pregnancy values (Figure 3).

Following labor, cardiac output further increases due to the relief of the inferior vena cava compression and autotransfusion from the uterus, as well as mobilization of the fluid from the extravascular space. In the first weeks postpartum cardiac output subsequently decreases and returns to pre-pregnancy values within 6 months after delivery 21,22 (Figure 3).
Figure 3. Hemodynamic changes in pregnancy, during labor and postpartum. Adapted from Cornetter and Ross-Hesselink\(^\text{23}\).

(CO, cardiac output; PVR, peripheral vascular resistance; MAP, mean arterial pressure)

Hemodynamic changes during pregnancy are physiological basis for cardiac remodeling. There is progressive increase in LV end-diastolic and end-systolic dimensions, wall thickness and mass, consistent with a more spherical shape of the LV and the development of eccentric remodeling or hypertrophy. There is an increase of left atrial dimensions reflecting an increased preload. These parameters gradually recover after delivery but may remain above normal values until 6 months postpartum\(^\text{21,24}\).

Data on LV function during pregnancy are relatively inconsistent, partly due to the non-uniform cardiovascular response to pregnancy among women\(^\text{21}\). However, different methodology, study population heterogeneity related to race, gestational age and anthropometric factors, measurement variability and load-dependency of echocardiographic parameters may explain the discrepancies in the results. Some authors reported preserved parameters of LV systolic function throughout pregnancy including ejection fraction, fractional shortening, tissue Doppler myocardial systolic velocity as well as strain parameter, a novel echocardiographic index of myocardial deformation\(^\text{25,26}\).
However, in other studies, the authors demonstrated a decrease in parameters of LV systolic function in the last trimester of pregnancy. The authors concluded that late pregnancy reduction of LV systolic indices reflects physiological adaptation to persistent increase in volume load.

Regarding echocardiographic parameters of diastolic function, the majority of data shows higher peak velocity of the early diastolic mitral inflow (E) and longer deceleration time (DT) of the E wave compared to non-pregnant women. In the last trimester, progressive increase in peak velocity of late diastolic mitral inflow (A) starts to dominate resulting in a decrease in E/A ratio. No change in the ratio of E wave and early diastolic myocardial velocity (e’) E/e’ which is an estimate of the LV filling pressure, has been found during pregnancy. In a study by Melchiorre, et al. who followed previous version of European recommendations for the evaluation of LV diastolic function, the authors found that almost one fifth of pregnancies at term met diagnostic criteria for diastolic dysfunction, mainly representative of impaired myocardial relaxation. Previous studies also reported altered pulsed wave and tissue Doppler diastolic parameters to some extent in late compared to earlier pregnancy. It has been postulated that impaired diastolic and systolic LV parameters observed in a proportion of women at the end of pregnancy may reflect cardiac maladaptation instead of normal physiological adaptation to chronic volume overload.

Cardiovascular changes in women with preeclampsia

Hemodynamic changes

Several studies have examined hemodynamic changes in women with preeclampsia, yet there is heterogeneity in results, which can be explained by methodological limitations and many confounding factors related to altered loading conditions. The hemodynamic abnormalities can range from high to low cardiac output and high to normal peripheral vascular resistance. It is believed that the most representative hemodynamic pattern in preeclampsia is low cardiac output and high peripheral vascular resistance reflecting high LV afterload. These data were demonstrated in the largest, prospective study using invasive hemodynamic monitoring with a Swan-Ganz pulmonary artery thermodilution catheter in untreated preeclamptic patients. In a large study of more than 600 subjects
using noninvasive monitoring with impedance cardiography the authors observed a gradual increase in peripheral vascular resistance and a gradual decrease in cardiac output from normal pregnancy to pregnancy-induced hypertension and preeclampsia group. The most increased peripheral vascular resistance and the most reduced cardiac output were observed in preeclamptic group with fetal growth restriction 38.

A hyperdynamic model of preeclampsia with high cardiac output was demonstrated in a longitudinal study of 400 primigravidas who were monitored during pregnancy with Doppler echocardiography. High cardiac output and normal peripheral vascular resistance were found during preclinical phase of the disease in women who developed preeclampsia; with the clinical onset of preeclampsia a shift to low cardiac output and high peripheral vascular resistance was noticed 39. Moreover, high cardiac output observed in some studies could also be the treatment effect, as the recruited patients were receiving antihypertensive medications, magnesium sulfate or intravenous fluids 37,40,41.

In a study by Valensise, et al. 42 the authors noted two different hemodynamic states in preclinical phase of preeclampsia: low cardiac output - high vascular resistance in women who developed early-onset preeclampsia (< 34 weeks of gestation) versus high cardiac output - low vascular resistance in late-onset preeclampsia (≥ 34 weeks of gestation). Other studies demonstrated that preeclampsia that occurs earlier in gestation and is associated with fetal growth restriction is related to low cardiac output and high peripheral vascular resistance, while in later and term gestation preeclampsia, fetuses tend to be larger and there is a high cardiac output, low peripheral vascular resistance and raised intravascular volume hemodynamic profile 43,44.

In accordance, recent data have shown that hemodynamic characteristics of preeclampsia seem associated with the presence or absence of fetal growth restriction rather than related to gestational age at onset; therefore, early-onset and late-onset preeclampsia cannot be considered as different disease processes 45. Fetal growth restriction was strongly associated with high peripheral vascular resistance whether or not in combination with preeclampsia. Preeclampsia without fetal growth restriction, however, had the same hemodynamic profile, namely high cardiac output, at late as well as early-onset 45. Fetal growth restriction more commonly coexists with preeclampsia at early gestation and is uncommon in late-onset preeclampsia, which could explain to some degree the results of previous studies 38,42,43,46,47.
Preeclampsia is also associated with arterial stiffness and endothelial dysfunction, which may persist after delivery. Intravascular volume in preeclampsia is thought to be depleted as a result of capillary leakage generated by endothelial dysfunction, rise in capillary hydrostatic pressure and decreased plasma oncotic pressure, predisposing preeclamptic women to pulmonary edema.

**Geometric and functional changes of the heart**

In response to increased LV afterload the heart in women with preeclampsia undergoes specific remodeling characterized by thicker LV wall and increased LV mass compared with healthy pregnant women. LV geometry changes tend to be more pronounced in women with early-onset preeclampsia.

Previous studies on LV systolic function were limited on conventional echocardiographic parameters which are very dependent on loading conditions. Some authors found reduced LV fractional shortening and ejection fraction in patients with preeclampsia compared with healthy pregnant women, whereas others showed no changes or even increased fractional shortening in conjunction with increased cardiac output. This was observed in untreated preeclamptic patients and explained by hyperdynamic model of preeclampsia. Bamfo, et al. found that longitudinal systolic myocardial velocity measured by tissue Doppler imaging, a relatively less load dependent index, was decreased in preeclamptic patients with fetal growth restriction similarly to normotensive fetal growth restriction pregnancies.

More recent studies have evaluated LV systolic function in preeclampsia with myocardial deformation imaging. Melchiorre, et al. who used tissue Doppler based technique, found no differences in global deformation indices between women who developed preeclampsia at term and healthy controls. However, more impaired deformation parameters and worse cardiac remodeling were detected in women with preterm or early-onset preeclampsia compared with those with preeclampsia at term or late-onset preeclampsia indicating preterm preeclampsia as a more severe form of the disease. Shahul, et al. assessed myocardial deformation by two-dimensional speckle tracking-derived method and demonstrated reduced global longitudinal strain (GLS) in women with preeclampsia compared with healthy pregnant women despite normal LV ejection fraction.
Furthermore, there is evidence that myocardial deformation may remain impaired also months after delivery \textsuperscript{63-65}. These findings may be consistent with epidemiological studies showing association between preeclampsia and subsequent cardiovascular risk \textsuperscript{1,66}.

Several studies have demonstrated impaired diastolic parameters in preeclampsia. The majority of data showed exaggerated reduction of the E/A ratio indicative of impaired myocardial relaxation \textsuperscript{53,57,61}. In some studies, increased E/e’ ratio was found, especially in early-onset preeclampsia, suggesting higher LV filling pressures \textsuperscript{53,67-69}. Melchiorre, et al. reported diastolic dysfunction defined by integration of diastolic parameters according to the previous version of the recommendations \textsuperscript{34} in 40\% of women with preeclampsia at term and even in 14\% of healthy controls \textsuperscript{60}. In a subsequent study the authors found that women with preterm preeclampsia have a more severe cardiac impairment than those with preeclampsia at term (26\% vs. 4\%; p < 0.05) \textsuperscript{61}. However, direct comparison of studies from the literature is difficult, as the timing of echocardiographic assessment in the studies was not comparable.

Additionally, there is also a lack of comprehensive analysis of time dependent changes in both hemodynamic and systolic and diastolic parameters in patients with preeclampsia before and after delivery.

**Management of preeclampsia with severe features**

The optimal management of a woman with preeclampsia depends on disease severity and gestational age. Preeclampsia with severe features is generally regarded as indication for delivery, which is the definite treatment of the disease and reduces the risks of maternal and fetal complications. Conservative antepartum management, which allows corticosteroid administration for fetal lung maturation and maternal transfer to a tertiary center with a neonatal intensive care unit, is an option in selected preeclamptic patients remote from term (at < 34 weeks of gestation). The essential tasks in the management of preeclamptic patients are blood pressure control and treatment of multiple-organ complications, which can also occur postpartum, particularly in the first 48 hours. For treatment and prevention of eclamptic seizures magnesium sulfate is the drug of choice as it has been shown to be more effective in comparison to placebo, no treatment, several psychotropic medications or an antihypertensive agent alone \textsuperscript{1}. Severe hypertension
(systolic blood pressure > 160 mmHg, diastolic blood pressure > 110 mmHg, or mean arterial pressure > 125 mmHg) should be treated in pregnant and puerperal patients to prevent stroke. Fluid management during preeclampsia is essential yet challenging and there are no prospective studies on which to base decisions regarding administration of fluids. Therefore, guidelines are largely based on consensus and retrospective data. Insufficient intravascular volume results in decreased oxygen delivery to tissues and exacerbates organ (including placental) dysfunction. On the other hand, fluid excesses can lead to fluid extravasation and pulmonary edema. Risk of fluid over-resuscitation is especially high in preeclampsia due to endothelial dysfunction and resulting increased vascular permeability. Due to immediate increase in cardiac output with mobilization of extravascular fluids following delivery, risk of pulmonary edema is also high in early postpartum period. In the nineties, acute pulmonary edema was the leading cause of death in women with preeclampsia. The Confidential Enquiry into Maternal Deaths in the UK reported six maternal deaths between 1994 and 1996 due to adult acute respiratory distress syndrome that appeared to be related to poor fluid management in women with preeclampsia. On the basis of these reported deaths, recommendations on limiting intravenous fluids to not more than to 80 ml/hour have been made. Higher rates may, however, be necessary in some preeclamptic patients to adequately correct tissue hypoperfusion.

**Non-invasive assessment of maternal hemodynamics**

Accurate assessment of maternal hemodynamics is fundamental for appropriate fluid management in patients with severe features of preeclampsia. Outside pregnancy, transthoracic cardiac ultrasound (echocardiography) and lung ultrasound have become important diagnostic and monitoring tools in critically ill patients. Echocardiography allows rapid and non-invasive assessment of myocardial function, preload and filling pressure, whereas lung ultrasound can be used to determine the amount of extravascular lung water. In pilot studies on smaller number of critically ill pregnant patients, non-invasive hemodynamic monitoring by echocardiography correlated well with invasive monitoring using a pulmonary artery catheter.
Previous studies have shown that both invasive hemodynamic monitoring and echocardiography in combination with lung ultrasound could facilitate fluid management in patients with preeclampsia. In critically ill patients, echocardiographic response of stroke volume to passive leg raising has been shown to predict fluid responsiveness. Fluid responsiveness is considered a state where an increase of venous return by fluid loading responses with an increase in stroke volume, indicating that a subject is at the steeper part of the Frank-Starling cardiac function curve. As a subject becomes less fluid responsive, there is a risk for marked increase in extravascular lung water and tissue edema, because increased cardiac filling pressures are transmitted to increased hydrostatic pressures. This process is accentuated in patients with endothelial damage, like in sepsis, burns and presumably also in preeclampsia. Predicting fluid responsiveness aims to optimize circulation and organ perfusion while avoiding potentially deleterious fluid administration in critically ill patients. Brun, et al. have demonstrated that in patients with severe preeclampsia fluid responsiveness can be predicted by an increase in the LV outflow tract velocity-time integral derived from the pulsed wave Doppler signal during passive leg raising.

THE AIM OF THE STUDY

The objective of this study was to assess whether echocardiographic parameters in combination with lung ultrasound can detect differences in hemodynamic status, cardiac function and lung congestion between patients with severe features of preeclampsia and control healthy women.

HYPOTHESES

1. Women with severe features of preeclampsia more frequently present with impaired parameters of diastolic LV function before and post-delivery in comparison with healthy pregnant women.
2. Women with severe features of preeclampsia have higher degree of lung congestion before and post-delivery in comparison with healthy pregnant women.

3. Women with severe features of preeclampsia are less fluid responsive compared to healthy pregnant controls.

4. In women with severe features of preeclampsia lung congestion is related to echocardiographic parameters of impaired diastolic function.

**METHODS**

This prospective, observational case control study was performed at a single tertiary perinatal center (Department of Perinatology, Division of Gynecology and Obstetrics, University Medical Center Ljubljana, Ljubljana, Slovenia) from April 2015 to April 2017. All women included in the study provided written informed consent for study participation. The National Medical Ethics Committee approved the study (Project number 83/09/14, approved on 09/16/2014).

**Study population**

Consecutively admitted women with singleton pregnancies complicated by preeclampsia with severe features were included in the study at hospital admission. Preeclampsia with severe features was defined by the American College of Obstetricians and Gynecologist Task Force on Hypertension in Pregnancy recommendations (Tables 1 and 2)\(^1\). Women were excluded if they had any comorbidities including chronic (pre-existent) or gestational hypertension, pre-existent or gestational diabetes mellitus, congenital or acquired heart disease or a history of tobacco smoking, alcohol or drug abuse during pregnancy. As per our institution’s standard protocol all patients were managed in a high dependency setting ante-partum and at least 24 hours post-delivery. Blood pressure was monitored continuously. Fluid intake and urine output were assessed hourly, and blood tests were repeated at least every 12 hours to monitor kidney function, electrolytes, full blood count, transaminases, and bilirubin. Magnesium sulfate was used for eclampsia prophylaxis as a 4 g intravenous loading dose, followed by 1 g/hour infusion.
Antihypertensive treatment with intravenous hydralazine or labetalol was used to maintain systolic blood pressure at < 160 mmHg and diastolic blood pressure at < 110 mmHg. Intravenous and oral fluid intake was minimized, and neither fluids nor diuretics were routinely administered to treat oliguria. Delivery has been pursued following maternal stabilization at gestational ages of ≥ 34 0/7 weeks. For patients at < 34 0/7 weeks of gestation, administration of a single course of antenatal corticosteroids was attempted and pregnancy managed expectantly for up to 48 hours in the absence of maternal and/or fetal indications for immediate delivery. Vaginal delivery was considered unless a caesarean delivery was required for the usual obstetric indications.

Controls were healthy pregnant women at term (≥ 37 0/7 weeks), matching the exclusion criteria cited above, with a singleton pregnancy and an estimated fetal weight appropriate for gestational age (AGA). They were included in the study at hospital admission for either planned cesarean section due to previous cesarean delivery or breech presentation or induction of labor.

**Study protocol**

At inclusion we measured body height and body weight of all participants. Body mass index was calculated by dividing body weight by the square of body height and body surface area was calculated using the Du Bois formula.

The study groups underwent echocardiographic examination and lung ultrasound at bedside before delivery (within 24 hours before delivery), 1 day post-delivery (within 24 hours post-delivery) and 4 days post-delivery. Systolic and diastolic blood pressures were measured at each examination in the semi-supine position with automatic oscillometric device on the right upper arm at the level of the heart. Fluid responsiveness was assessed before delivery (within 24 hours before delivery) and one day post-delivery (within 24 hours post-delivery) (Figure 4).
For additional analysis, the group of preeclamptic patients was further divided according to an estimated fetal weight into small for gestational age (SGA) and AGA. SGA was defined as a neonate with birth weight < 5th centile for gestational age.

**Ultrasound examination**

Ultrasound examination was performed using Vivid S6 scanner (GE Vingmed Ultrasound, AS, Horten, Norway) with a 3Sc-RC cardiac transducer for both echocardiography and lung ultrasound. All images were stored digitally for later offline analysis using dedicated software (EchoPac version 201; GE Vingmed Ultrasound AS).

**Echocardiographic examination**

Participants were studied at rest in the left lateral decubitus position and data acquired at end expiration from standard parasternal and apical windows. Heart rate was obtained during each echocardiogram. Standard two-dimensional and Doppler echocardiography
were performed according to the joint recommendations of the American Society of Echocardiography and European Association of Echocardiography \textsuperscript{91}.

\textit{Hemodynamic characteristics}

LV stroke volume was calculated as the product of LV outflow tract area and LV outflow tract velocity-time integral (VTI) derived from the pulsed wave Doppler signal in the LV outflow tract [equation (1)]. LV outflow tract area was calculated using the [equation (2)] \textsuperscript{91}. Additionally, we calculated cardiac output [equation (3)], mean arterial pressure [equation (4)], peripheral vascular resistance [equation (5)] and stroke work [equation (6)] \textsuperscript{92}.

\begin{align*}
\text{LV SV} &= \text{LVOT area} \times \text{VTI} \quad (1) \\
\text{LVOT area} &= (\text{LVOT D})^2 \times \pi/4 \quad (2) \\
\text{CO} &= \text{LV SV} \times \text{HR} \quad (3) \\
\text{MAP} &= \left[\text{systolic blood pressure} + (2 \times \text{diastolic blood pressure})\right]/3 \quad (4) \\
\text{PVR} &= 80 \times \text{MAP} / \text{CO} \quad (5) \\
\text{SW} &= \text{MAP} \times \text{SV} \quad (6)
\end{align*}

(LV SV, left ventricular stroke volume; LVOT, left ventricular outflow tract; VTI, left ventricular outflow tract velocity-time integral; LVOT D, left ventricular outflow diameter; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PVR, peripheral vascular resistance; SW, stroke work)

\textit{Cardiac geometry}

Parasternal long-axis measurements included LV internal diameter at end diastole (LVEDD) and at end systole (LVESD), interventricular septal wall thickness at end diastole (IVS), inferolateral wall thickness at end diastole (INF-LAT), and the LV outflow tract diameter measured in mid-systole. LV dimensions were measured directly on two-dimensional images to avoid oblique sections of the LV and diameter overestimation when using M-mode approach. LV mass was calculated from linear LV dimensions using
the appropriate formula proposed by Lang, et al. Relative wall thickness (RWT) was calculated as the ratio of two times INF-LAT to LVEDD. Concentric remodeling was defined as RWT of > 0.42 and a normal LV mass index (≤ 95 g/m²). Concentric and eccentric LV hypertrophy was defined as increased LV mass (LV mass index > 95 g/m² and/or LV mass > 162 g) with RWT > 0.42 and RWT ≤ 0.42, respectively.

LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes as well as left atrial end-systolic volumes were measured in the apical 4- and 2-chamber views using the Simpson biplane method. LV sphericity index was calculated as the ratio of major LV internal diameter and minor LV internal diameter in apical 4-chamber view.

*Left ventricular systolic and diastolic function*

Using conventional echocardiographic parameters LV systolic function was assessed by calculating LV ejection fraction as the ratio of LV stroke volume and LV end-diastolic volume. Additionally, using M-mode in the apical 4-chamber view we measured mitral septal (MAPSE_{med}) and mitral lateral (MAPSE_{lat}) annular plane systolic excursions. Tissue Doppler imaging was used to measure peak systolic myocardial velocities at the septal (s’_{med}) and lateral (s’_{lat}) mitral annulus.

LV diastolic parameters were obtained by pulsed wave Doppler in the apical 4-chamber view. At the tips of the mitral leaflets we measured mitral inflow velocities E and A, deceleration time (DT) of the E wave and calculated E/A ratio. Tissue Doppler imaging was used to measure early diastolic myocardial velocities at the septal (e’_{med}) and lateral (e’_{lat}) mitral annulus in the apical 4-chamber view. All measurements obtained by Doppler imaging were averaged from three consecutive cardiac cycles. Septal and lateral early diastolic velocity values were averaged and denoted by e’. The ratio E/e’ was calculated as E divided by e’ and was used as an estimation of LV filling pressure.

In addition to standard diastolic parameters the ratio of early diastolic and systolic myocardial velocities (e’/s’) was calculated as it was proposed as an earlier parameter of impaired myocardial relaxation in clinical states where systolic function and filling pressures are normal.
**Myocardial deformation parameters**

For myocardial deformation analysis two-dimensional echocardiographic images were acquired together with a simultaneous ECG signal from the apical 2-, 3- and 4-chamber views. Five consecutive cardiac cycles were recorded and digitally stored for offline analysis using manual two-dimensional speckle-tracking analysis software (EchoPac version 201; GE Vingmed Ultrasound, AS). The images with the highest quality with no less than 60 frames per second and the most optimal endocardial delineation were selected for analysis. The endocardial border was traced manually in the apical 2-, 3-, and 4-chamber views, adjusting the width of the region of interest to the myocardial wall thickness. Manual adjustments were made after visual inspection of the segmental tracking results throughout the cardiac cycle, with the goal of obtaining the best possible tracking in all myocardial segments. Segments with inadequate tracking were excluded from further analysis. Images with insufficient tracking in > 3 segments per LV were excluded from analysis. For data evaluation, LV was divided in 6 segments in each view and segmental strain was calculated for each of the 18 segments. GLS was defined as the average of the peak systolic strain values in all myocardial segments; more negative values indicating higher myocardial deformation. For data analysis we used absolute values of peak systolic mid-wall GLS. Global early diastolic strain rate (SRe) was calculated from the average of all 18 segments. The E/SRe ratio, as a marker of LV filling pressure, was calculated as E divided by the global SRe value.

Opening and closure of aortic and mitral valves based on pulsed wave Doppler tracings were used to determine time intervals.

**Lung ultrasound**

Lung ultrasound was performed according to a systematic protocol in supine position\(^{74,76}\). The Echo Comet Score (ECS) was obtained by the 28-rib interspaces technique dividing the chest wall in 12 areas on the left (from the second to the fourth intercostal space) and 16 areas on the right (from the second to the fifth intercostal space) anterior and lateral hemithorax\(^{76}\) (Figure 5). The amount of extravascular lung water was assessed by the number of B-lines or “comet tails”\(^ {75} \). B-lines are defined as discrete laser-like vertical
hyperechoic reverberation artefacts that arise from the pleural line and extend to the bottom of the screen without fading and move synchronously with lung sliding. They represent a reverberation artefact through edematous interlobular septa or alveoli \(^{75,76}\). The sum of B-lines found on each of the 28 chest wall areas yields the ECS denoting the amount of extravascular lung water \(^{76}\).

Figure 5. Distribution and the serial numbers of the 28-rib interspaces on the chest wall for assessment of the Echo Comet Score.
**Fluid responsiveness**

Fluid responsiveness was assessed by measuring changes in LV stroke volume (ΔSV) while performing passive leg rising (PLR) to a 45° angle for two minutes. LV stroke volume was calculated using [equation (1)]. LV outflow diameter was measured once, since it remains constant in a given subject. A second measurement of VTI was obtained within 30 seconds after the end of PLR and was compared with the baseline value. Fluid responsiveness was defined as a ΔSV of ≥ 12% \(^{85,87,94}\).

**Statistical analysis**

For continuous variables, data were expressed as median together with the 25\(^{th}\) and 75\(^{th}\) percentiles (inter-quartile range). Categorical data were summarized as frequencies and percentages. For comparison between the study groups (severe preeclampsia vs. controls) and preeclamptic patients with SGA vs. AGA fetuses, Mann Whitney U-test was used for continuous variables and Chi-square test or Fisher’s exact test for categorical variables, as appropriate. Changes in parameters over time (before delivery vs. 1 day post-delivery vs. 4 days post-delivery) within each group were analyzed by repeated-measures ANOVA. Measurements before delivery vs. 1 day post-delivery, and 1 day post-delivery vs. 4 days post-delivery within each group were compared by Wilcoxon Signed Ranks test. Spearman’s correlation analysis was used to assess the relationship between ECS and diastolic function parameters. For all tests, a two-tailed \(p\) value ≤ 0.05 was considered statistically significant. The software used for statistical analysis was IBM SPSS Statistics for Windows Version 21.0 (Armonk, NY: IBM Corp.).

**RESULTS**

**Study population characteristics**

Thirty women with preeclampsia with severe features and 30 healthy controls were included in the study; characteristics of the participants are shown in Table 3. No statistically significant differences were found among the two groups regarding age, body
mass index before pregnancy and body mass index and body surface area at inclusion. Maternal ethnicity was Caucasian except for one woman in preeclamptic group, who was Asian. There were more nulliparous women in preeclamptic than in control group (p < 0.001). None of the multiparous women had had preeclampsia or delivered preterm in their previous pregnancy. As expected from the study design, gestational age was higher in the control group (p < 0.001). There was a statistically non-significant trend towards a higher proportion of SGA neonates in preeclamptic group (p = 0.195). In the majority of participants (80% in preeclamptic vs. 87% in control group, p = 0.515) Cesarean section was performed. The high rate of Cesarean section among controls was a reflection of the criteria used for inclusion in this group.

Table 3. Study population characteristics. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>30 (24 - 36)</td>
<td>32 (28 - 36)</td>
<td>0.176</td>
</tr>
<tr>
<td>BMI at inclusion (kg/m²)</td>
<td>28.9 (27.3 - 31.4)</td>
<td>28.0 (25.6 - 32.1)</td>
<td>0.464</td>
</tr>
<tr>
<td>BMI before pregnancy (kg/m²)</td>
<td>23.6 (21.3 - 26.6)</td>
<td>23.0 (19.7 - 25.8)</td>
<td>0.433</td>
</tr>
<tr>
<td>Nulliparous (n, %)</td>
<td>25 (83)</td>
<td>7 (23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>32 5/7 (22 3/7 - 39 4/7)</td>
<td>38 3/7 (37 0/7 - 42 1/7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cesarean delivery (n, %)</td>
<td>24 (80)</td>
<td>26 (87)</td>
<td>0.515</td>
</tr>
<tr>
<td>SGA (n, %)</td>
<td>5 (17)</td>
<td>1 (3)</td>
<td>0.195</td>
</tr>
</tbody>
</table>

(BMI, body mass index; SGA, small for gestational age)

Severe features of preeclampsia were: hypertension in all 30 (100%) cases; neurological symptoms in 14 (46%); visual disturbances in 4 (4%); elevated liver enzymes in 10 (33%); thrombocytopenia in 3 (10%); and right upper abdominal pain in 5 (16%) patients. In the preeclampsia group, all 30 patients were treated with magnesium sulfate as per our institution’s protocol before delivery as well as at 24 h post-delivery. Magnesium sulfate
was, therefore, administered as a continuous intravenous infusion of 1 g/h (as a 50 mL/h infusion) during the first two sonographic examinations: before delivery and 1 day post-delivery. In 24 (80%) women with preeclampsia, magnesium sulfate was the only intravenous fluid intake. In 6 (20%) patients with preeclampsia, an additional 30 mL/hour infusion of crystalloids was administered before delivery and during the first ultrasound examination, while always limiting administration of intravenous fluid to 80 mL/h. Intravenous hydralazine was necessary for blood-pressure control in 6 (20%) women with preeclampsia before delivery. On day 4 postpartum, no woman with preeclampsia was receiving any intravenous fluid or medication. No woman in the control group received intravenous medication or intravenous fluid at the time of the sonographic examinations.

**Hemodynamic characteristics**

Hemodynamic parameters of the study population before delivery are reported in Table 4. As expected, women with severe features of preeclampsia had significantly higher systolic, diastolic and mean arterial pressures concomitant with higher peripheral vascular resistance and stroke work compared with control subjects (p ≤ 0.001, respectively), while heart rate was comparable between both groups. No differences in stroke volumes and cardiac output were found between the groups. Similar differences in hemodynamic parameters between both groups were also noted 1 day and 4 days post-delivery.
Table 4. Hemodynamic characteristics of the study population before delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>151 (136 - 159)</td>
<td>118 (111 - 124)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>90 (86 - 100)</td>
<td>75 (69 - 82)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>110 (103 - 119)</td>
<td>88 (81 - 96)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>77 (70 - 89)</td>
<td>75 (69 - 84)</td>
<td>0.736</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>70 (61 - 78)</td>
<td>68 (57 - 76)</td>
<td>0.194</td>
</tr>
<tr>
<td>SV index (ml/m²)</td>
<td>37 (33 - 41)</td>
<td>36 (33 - 40)</td>
<td>0.195</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>5.5 (4.9 - 6.2)</td>
<td>5.0 (4.4 - 5.9)</td>
<td>0.312</td>
</tr>
<tr>
<td>CI (ml/m²/min)</td>
<td>2.9 (2.6 - 3.3)</td>
<td>2.8 (2.4 - 3.2)</td>
<td>0.269</td>
</tr>
<tr>
<td>Stroke work (mmHg×ml)</td>
<td>7947 (6865 - 8588)</td>
<td>5873 (5109 - 6451)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PVR (dynes×s×cm⁻⁵)</td>
<td>1694 (1480 - 1871)</td>
<td>1411 (1173 - 1612)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

(SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SV, stroke volume; CO, cardiac output; CI, cardiac index; PVR, peripheral vascular resistance)

There were no statistically significant differences in hemodynamic parameters when comparing preeclamptic patients with SGA vs. AGA neonates before delivery (mean arterial pressure: 110 (92 - 119) mmHg vs. 110 (105 – 120) mmHg, p = 0.269; cardiac output: 5.1 (4.0 – 5.2) ml/min vs. 5.6 (5.0 – 6.4) ml/min, p = 0.057; peripheral vascular resistance: 1874 (1588 - 2059) dynes×s×cm⁻⁵ vs. 1643 (1440 - 1799) dynes×s×cm⁻⁵, p = 0.205) as well as on day 1 post-delivery (mean arterial pressure: 101 (97 – 112) mmHg vs. 112 (107 – 117) mmHg, p = 0.073; cardiac output: 5.0 (3.7 – 5.9) ml/min vs. 4.9 (4.0 – 6.2) ml/min, p = 0.698; peripheral vascular resistance: 1588 (1328 - 2415) dynes×s×cm⁻⁵ vs. 1770 (1529 - 1799) dynes×s×cm⁻⁵, p = 0.842). On day 4 post-delivery, however, cardiac output was significantly lower and peripheral vascular resistance significantly higher in SGA preeclamptic pregnancies compared to those with AGA fetuses/neonates: cardiac output: 3.7 (3.2 – 4.2) ml/min vs. 5.0 (4.4 – 5.8) ml/min, p = 0.007; peripheral vascular resistance: 2504.0 (2245.0 - 2763.0) dynes×s×cm⁻⁵ vs. 1793.5 (1424.1 - 2162.4)
Mean arterial pressure did not significantly differ on day 4 post-delivery between SGA and AGA groups: 108 (102 - 108) mmHg vs. 106 (103 – 115) mmHg, p = 0.990.

In the SGA group, there were no significant differences in mean arterial pressure (p = 0.805, ANOVA), cardiac output (p = 0.131, ANOVA), and peripheral vascular resistance (p = 0.098, ANOVA) when comparing measurements before vs. 1 day vs. 4 days post-delivery. Similarly, there were no significant differences over time in the AGA group (p = 0.716 for mean arterial pressure; p = 0.157 for cardiac output; and p = 0.129 for peripheral vascular resistance).

**Cardiac geometry**

Parameters of cardiac geometry before delivery are reported in Table 5. Women with severe features of preeclampsia had thicker IVS (p = 0.036) and INF-LAT (p = 0.043) wall, higher LV mass (p = 0.026) and LV mass index (p < 0.001) compared with controls. However, no significant differences in relative wall thickness, LV dimensions and sphericity index were detected between both groups. In the group of preeclampsia higher number of women showed LV remodeling compared with control group (p = 0.028). Left atrial volumes and volume indices were significantly larger in preeclamptic group than in controls (all p < 0.001). Similar differences in cardiac geometric parameters between both groups were noted 1 day and 4 days post-delivery except for the lower LVEDV 1 day post-delivery in the control group (median [interquartile range]: 100.0 ml (92.0 - 104.5 ml) vs. 115.5 ml (101.0 – 127.8 ml), p < 0.001).
Table 5. Cardiac dimensions of the study population before delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>47 (44 - 52)</td>
<td>47 (45 - 51)</td>
<td>0.801</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>30 (26 - 32)</td>
<td>31 (29 - 32)</td>
<td>0.106</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>9.0 (8.0 - 10.0)</td>
<td>9.0 (7.8 - 9.0)</td>
<td>0.036</td>
</tr>
<tr>
<td>INFLAT (mm)</td>
<td>9.0 (8.0 - 10.3)</td>
<td>8.0 (8.0 - 9.0)</td>
<td>0.043</td>
</tr>
<tr>
<td>RWT</td>
<td>0.39 (0.32 - 0.44)</td>
<td>0.36 (0.33 - 0.39)</td>
<td>0.123</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>142 (121 - 171)</td>
<td>130 (120 - 147)</td>
<td>0.026</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>76 (71 - 90)</td>
<td>70 (66 - 75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac geometry</td>
<td></td>
<td></td>
<td>0.028</td>
</tr>
<tr>
<td>Normal geometry (n, %)</td>
<td>16 (53)</td>
<td>28 (94)</td>
<td></td>
</tr>
<tr>
<td>Concentric remodeling (n, %)</td>
<td>5 (17)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Concentric hypertrophy (n, %)</td>
<td>4 (13)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Eccentric hypertrophy (n, %)</td>
<td>5 (17)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>107.5 (91.5 - 124.3)</td>
<td>104.0 (93.8 - 116.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>LVEDV index (ml/m²)</td>
<td>55.5 (51.8 - 63.0)</td>
<td>55.5 (52.0 - 61.3)</td>
<td>0.631</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>34.5 (28.5 - 44.5)</td>
<td>37.5 (31.8 - 42.0)</td>
<td>0.451</td>
</tr>
<tr>
<td>LVESV index (ml/m²)</td>
<td>18.5 (16.0 - 22.0)</td>
<td>20.0 (17.0 - 22.3)</td>
<td>0.337</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>1.69 (1.56 - 1.86)</td>
<td>1.73 (1.58 - 1.84)</td>
<td>0.871</td>
</tr>
<tr>
<td>LA volume (ml)</td>
<td>58.5 (50.8 - 69.3)</td>
<td>50.5 (45.0 - 57.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>LA volume index (ml/m²)</td>
<td>32.5 (29.0 - 36.0)</td>
<td>27.0 (25.5 - 31.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

(LVEDD, left ventricular internal end-diastolic diameter; LVESD, left ventricular internal end-systolic diameter; IVS, interventricular septal wall thickness at end diastole, INFLAT, inferolateral wall thickness at end diastole; RWT, relative wall thickness, calculated as the ratio: 2 × INFLAT/LVEDD; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LA, left atrium)
According to parameters of cardiac geometry, only left atrial volume before delivery was significantly different between AGA and SGA preeclamptic pregnancies (AGA: 63.0 (51.2 - 74.8) ml vs. SGA: 49.0 (41.7 - 56.3) ml; p = 0.022). There was also a trend, although not statistically significant, towards higher atrial volumes in AGA pregnancies on day 1 post-delivery (65.0 (54.6 - 75.4) ml vs. 58.0 (51.9 - 64.1) ml; p = 0.078) and on day 4 post-delivery (64.0 (54.1 - 73.9) ml vs. 56.0 (48.2 - 63.8); p = 0.055).

**Left ventricular systolic and diastolic function**

LV systolic and diastolic function parameters before delivery, 1 day and 4 days post-delivery are presented in Tables 6-8.

Women with severe features of preeclampsia had lower peak systolic myocardial velocities compared with controls at all assessments; the differences became statistically significant 4 days post-delivery for both septal and lateral mitral velocities; p = 0.001 and p = 0.04, respectively. Values of ejection fraction and MAPSE at the septal and lateral mitral annulus were similar between the groups at all assessments.

Within preeclamptic and control group there were no significant changes in ejection fraction values over time (p = 0.55 and p = 0.61, respectively, ANOVA).

Diastolic function parameters showed differences between preeclamptic and control group that were significant at certain assessments: higher A velocities (before delivery, p < 0.001; 1 day post-delivery, p = 0.022), lower E/A ratio (before delivery, p = 0.042) and longer DT (1 day post-delivery, p = 0.043; 4 days post-delivery, p = 0.019) in severe preeclampsia group. Overall e’ velocities at both septal and lateral mitral annulus were lower in women with preeclampsia than in controls (all p < 0.001 with an exception of e’_{med} before delivery, p = 0.062). E/e’_{med}, E/e’_{lat} and E/e’ ratios were significantly higher in women with preeclampsia than in controls at all assessments (all p < 0.001) (Figure 6).

In preeclamptic group, there were significant differences in the E/e’ ratios over time (p = 0.02, ANOVA) (Figure 6). E/e’ values were significantly higher 1 day post-delivery than before delivery (p = 0.001) or 4 days post-delivery (p = 0.001). In controls, no such
change was observed (p = 0.85, ANOVA). Figure 7 presents echocardiographic assessment of the E/e’ ratio in a representative preeclamptic woman and a healthy control.

The ratios e’/s’ for septal and lateral mitral annulus were lower in preeclamptic group than in controls at all assessments; the difference was significant for lateral e’<sub>lat</sub>/s’<sub>lat</sub> 1 day (p = 0.003) and 4 days post-delivery (p = 0.042).

There were no significant differences in LV systolic and diastolic function parameters in preeclamptic patients with SGA vs. AGA fetuses/neonates.
Table 6. Left ventricular systolic and diastolic function parameters of the study population before delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic function parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>66 (64 - 71)</td>
<td>66 (61 - 67)</td>
<td>0.061</td>
</tr>
<tr>
<td>MAPSE&lt;sub&gt;med&lt;/sub&gt; (mm)</td>
<td>12.7 (11.6 - 14.4)</td>
<td>13.7 (12.5 - 14.7)</td>
<td>0.126</td>
</tr>
<tr>
<td>MAPSE&lt;sub&gt;lat&lt;/sub&gt; (mm)</td>
<td>16.1 (14.5 - 17.8)</td>
<td>16.0 (14.4 - 17.5)</td>
<td>0.865</td>
</tr>
<tr>
<td>s'&lt;sub&gt;med&lt;/sub&gt; (cm/s)</td>
<td>7.7 (7.1 - 9.0)</td>
<td>8.3 (7.8 - 8.7)</td>
<td>0.178</td>
</tr>
<tr>
<td>s'&lt;sub&gt;lat&lt;/sub&gt; (cm/s)</td>
<td>8.6 (7.6 - 9.6)</td>
<td>9.3 (8.4 - 10.4)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Diastolic function parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>83 (67 - 97)</td>
<td>70 (61 - 81)</td>
<td>0.086</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>58 (49 - 71)</td>
<td>41 (38 - 52)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/A</td>
<td>1.27 (1.10 - 1.66)</td>
<td>1.58 (1.28 - 2.07)</td>
<td>0.042</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>180 (138 - 201)</td>
<td>184 (159 - 198)</td>
<td>0.616</td>
</tr>
<tr>
<td>e'&lt;sub&gt;med&lt;/sub&gt; (cm/s)</td>
<td>8.7 (7.0 - 10.3)</td>
<td>9.0 (8.2 - 10.7)</td>
<td>0.062</td>
</tr>
<tr>
<td>e'&lt;sub&gt;lat&lt;/sub&gt; (cm/s)</td>
<td>11.0 (9.1 - 12.8)</td>
<td>12.8 (11.0 - 14.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>E/e'&lt;sub&gt;med&lt;/sub&gt;</td>
<td>9.6 (7.6 - 11.1)</td>
<td>7.4 (6.2 - 9.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>E/e'&lt;sub&gt;lat&lt;/sub&gt;</td>
<td>7.2 (5.6 - 9.3)</td>
<td>5.4 (4.8 - 6.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>E/e’</td>
<td>8.2 (6.3 - 10.1)</td>
<td>6.3 (5.3 - 7.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>e'&lt;sub&gt;med&lt;/sub&gt;/s'&lt;sub&gt;med&lt;/sub&gt;</td>
<td>1.07 (0.92 - 1.24)</td>
<td>1.13 (0.96 - 1.30)</td>
<td>0.300</td>
</tr>
<tr>
<td>e'&lt;sub&gt;lat&lt;/sub&gt;/s'&lt;sub&gt;lat&lt;/sub&gt;</td>
<td>1.29 (1.05 - 1.50)</td>
<td>1.35 (1.21 - 1.49)</td>
<td>0.246</td>
</tr>
</tbody>
</table>

(EF, ejection fraction; MAPSE<sub>med</sub>, mitral septal annular plane systolic excursion; MAPSE<sub>lat</sub>, mitral lateral septal annular plane systolic excursion; s’<sub>med</sub>, peak systolic myocardial velocity at the septal mitral annulus; s’<sub>lat</sub>, peak systolic myocardial velocity at the lateral mitral annulus; E, peak early diastolic mitral inflow velocity; A, peak late diastolic mitral inflow velocity; DT, deceleration time of the E wave; e’<sub>med</sub>, peak early diastolic myocardial velocity at the septal mitral annulus; e’<sub>lat</sub>, peak early diastolic myocardial velocity at the lateral mitral annulus; E/e’, ratio of the E and average of the septal and lateral e’ velocities)
Table 7. Left ventricular systolic and diastolic function parameters of the study population 1 day post-delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic function parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>65 (62 - 70)</td>
<td>64 (62 - 66)</td>
<td>0.09</td>
</tr>
<tr>
<td>MAPSE\textsubscript{med} (mm)</td>
<td>12.8 (11.7 - 14.5)</td>
<td>13.0 (12.5 - 14.2)</td>
<td>0.487</td>
</tr>
<tr>
<td>MAPSE\textsubscript{lat} (mm)</td>
<td>16.4 (14.8 - 17.4)</td>
<td>15.9 (14.3 - 16.5)</td>
<td>0.194</td>
</tr>
<tr>
<td>s'\textsubscript{med} (cm/s)</td>
<td>7.5 (6.5 - 8.1)</td>
<td>7.9 (7.5 - 8.7)</td>
<td>0.012</td>
</tr>
<tr>
<td>s'\textsubscript{lat} (cm/s)</td>
<td>7.7 (6.9 - 8.9)</td>
<td>8.4 (7.3 - 9.3)</td>
<td>0.085</td>
</tr>
<tr>
<td><strong>Diastolic function parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>91 (75 - 100)</td>
<td>83 (76 - 93)</td>
<td>0.41</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>53 (45 - 69)</td>
<td>45 (40 - 56)</td>
<td>0.022</td>
</tr>
<tr>
<td>E/A</td>
<td>1.59 (1.31 - 2.03)</td>
<td>1.76 (1.55 - 2.02)</td>
<td>0.112</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>171 (152 - 202)</td>
<td>160 (139 - 174)</td>
<td>0.043</td>
</tr>
<tr>
<td>e'\textsubscript{med} (cm/s)</td>
<td>8.2 (7.2 - 9.6)</td>
<td>9.8 (8.7 - 11.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>e'\textsubscript{lat} (cm/s)</td>
<td>10.9 (9.3 - 13.1)</td>
<td>14.1 (12.3 - 15.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/e'\textsubscript{med}</td>
<td>10.4 (9.0 - 12.1)</td>
<td>7.9 (7.2 - 10.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>E/e'\textsubscript{lat}</td>
<td>7.7 (6.4 - 9.0)</td>
<td>5.9 (5.5 - 6.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>E/e'</td>
<td>8.6 (7.6 - 10.2)</td>
<td>6.9 (6.2 - 7.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>e'/s'\textsubscript{med}</td>
<td>1.14 (1.03 - 1.30)</td>
<td>1.22 (1.13 - 1.33)</td>
<td>0.081</td>
</tr>
<tr>
<td>e'/s'\textsubscript{lat}</td>
<td>1.43 (1.27 - 1.64)</td>
<td>1.64 (1.52 - 1.78)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

(EF, ejection fraction; MAPSE\textsubscript{med}, mitral septal annular plane systolic excursion; MAPSE\textsubscript{lat}, mitral lateral septal annular plane systolic excursion; s'\textsubscript{med}, peak systolic myocardial velocity at the septal mitral annulus; s'\textsubscript{lat}, peak systolic myocardial velocity at the lateral mitral annulus; E, peak early diastolic mitral inflow velocity; A, peak late diastolic mitral inflow velocity; DT, deceleration time of the E wave; e'\textsubscript{med}, peak early diastolic myocardial velocity at the septal mitral annulus; e'\textsubscript{lat}, peak early diastolic myocardial velocity at the lateral mitral annulus; E/e’, ratio of the E and average of the septal and lateral e’ velocities)
Table 8. Left ventricular systolic and diastolic function parameters of the study population 4 days post-delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systolic function parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>64 (60 - 71)</td>
<td>65 (60 - 69)</td>
<td>0.592</td>
</tr>
<tr>
<td>MAPSE&lt;sub&gt;med&lt;/sub&gt; (mm)</td>
<td>12.7 (11.0 - 13.9)</td>
<td>13.5 (12.7 - 15.0)</td>
<td>0.865</td>
</tr>
<tr>
<td>MAPSE&lt;sub&gt;lat&lt;/sub&gt; (mm)</td>
<td>15.6 (14.6 - 17.0)</td>
<td>15.8 (14.6 - 17.0)</td>
<td>0.614</td>
</tr>
<tr>
<td>s'&lt;sub&gt;med&lt;/sub&gt; (cm/s)</td>
<td>7.4 (6.6 - 7.8)</td>
<td>8.1 (7.9 - 9.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>s'&lt;sub&gt;lat&lt;/sub&gt; (cm/s)</td>
<td>8.1 (7.3 - 9.0)</td>
<td>8.7 (8.0 - 9.7)</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Diastolic function parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>80 (69 - 93)</td>
<td>82 (76 - 86)</td>
<td>0.712</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>53 (47 - 63)</td>
<td>48 (44 - 55)</td>
<td>0.255</td>
</tr>
<tr>
<td>E/A</td>
<td>1.43 (1.14 - 1.79)</td>
<td>1.65 (1.42 - 1.97)</td>
<td>0.172</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>181 (159 - 218)</td>
<td>162 (133 - 189)</td>
<td>0.019</td>
</tr>
<tr>
<td>e'&lt;sub&gt;med&lt;/sub&gt; (cm/s)</td>
<td>8.5 (7.7 - 9.6)</td>
<td>10.3 (9.0 - 12.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>e'&lt;sub&gt;lat&lt;/sub&gt; (cm/s)</td>
<td>11.1 (9.9 - 13.1)</td>
<td>13.6 (12.2 - 15.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/e'&lt;sub&gt;med&lt;/sub&gt;</td>
<td>9.6 (8.0 - 10.5)</td>
<td>7.7 (6.8 - 8.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>E/e'&lt;sub&gt;lat&lt;/sub&gt;</td>
<td>7.1 (8.9 - 8.5)</td>
<td>5.7 (5.0 - 6.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>E/e’</td>
<td>8.3 (7.1 - 9.0)</td>
<td>6.8 (5.9 - 7.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>e'&lt;sub&gt;med&lt;/sub&gt;/s'&lt;sub&gt;med&lt;/sub&gt;</td>
<td>1.16 (1.00 - 1.28)</td>
<td>1.19 (1.09 - 1.50)</td>
<td>0.094</td>
</tr>
<tr>
<td>e'&lt;sub&gt;lat&lt;/sub&gt;/s'&lt;sub&gt;lat&lt;/sub&gt;</td>
<td>1.37 (1.14 - 1.69)</td>
<td>1.55 (1.38 - 1.77)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

(EF, ejection fraction; MAPSE<sub>med</sub>, mitral septal annular plane systolic excursion; MAPSE<sub>lat</sub>, mitral lateral septal annular plane systolic excursion; s'<sub>med</sub>, peak systolic myocardial velocity at the septal mitral annulus; s'<sub>lat</sub>, peak systolic myocardial velocity at the lateral mitral annulus; E, peak early diastolic mitral inflow velocity; A, peak late diastolic mitral inflow velocity; DT, deceleration time of the E wave; e'<sub>med</sub>, peak early diastolic myocardial velocity at the septal mitral annulus; e'<sub>lat</sub>, peak early diastolic myocardial velocity at the lateral mitral annulus; E/e’, ratio of the E and average of the septal and lateral e’ velocities)
Figure 6. Comparison of the E/e’ ratios in preeclampsia with severe features and control groups. E/e’ was higher in preeclamptic patients before delivery (p = 0.002), 1 day post-delivery (p = 0.001), and 4 days post-delivery (p = 0.003). Changes in the E/e’ ratio over time were significant in preeclamptic (p = 0.02), but not in control group (p = 0.85); * represents statistical significance. Data are presented with box-whisker plots with median and interquartile range and minimum and maximum data points.

(E/e’, ratio of the E and average of the septal and lateral e’ velocities)
Figure 7. A representative example of pulsed wave Doppler (a, c) and tissue Doppler (b, d) curves in a study woman with preeclampsia with severe features (a, b) and a healthy control (c, d). Note the higher ratio of the peak velocity of early diastolic mitral inflow (E) to peak early diastolic myocardial velocity at the septal mitral annulus (e’) in a preeclamptic woman (E/e’ = 13.1) compared to the ratio in a healthy control (E/e’ = 7.8).

**Myocardial deformation parameters**

Myocardial deformation parameters differed between women with severe features of preeclampsia and controls (Tables 9-11). However, GLS values were significantly lower in preeclamptic group only 4 days post-delivery (p = 0.027). Figure 8 presents longitudinal systolic strain curves in a study woman with preeclampsia with severe features. In preeclamptic group there were no significant changes in GLS values over time (p = 0.28, ANOVA). Similarly, there were no significant changes in GLS values over time in controls (p = 0.09, ANOVA).
Lower values were also obtained for SRe in preeclamptic group with significant differences before delivery (p = 0.015) and 4 days post-delivery (p = 0.02). Figure 9 presents longitudinal diastolic strain rate curves in a study healthy woman. Significant difference in E/SRe ratio was found only before delivery (p = 0.008), with higher values in preeclamptic women.

Table 9. Myocardial deformation parameters of the study population before delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS (%)</td>
<td>–21.5 (–23.4 to –20.3)</td>
<td>–22.2 (–23.3 to –21.1)</td>
<td>0.482</td>
</tr>
<tr>
<td>SRe (s⁻¹)</td>
<td>1.81 (1.61 - 2.20)</td>
<td>2.11 (1.96 - 2.31)</td>
<td>0.015</td>
</tr>
<tr>
<td>E/SRe (cm/s²)</td>
<td>40.1 (36.3 - 46.9)</td>
<td>32.8 (27.0 - 38.7)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

(GLS, global longitudinal strain; SRe, global early diastolic strain rate; E, peak early diastolic mitral inflow velocity)

Table 10. Myocardial deformation parameters of the study population 1 day post-delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS (%)</td>
<td>–21.4 (–22.4 to –20.7)</td>
<td>–21.6 (–23.1 to –20.6)</td>
<td>0.644</td>
</tr>
<tr>
<td>SRe (s⁻¹)</td>
<td>2.14 (1.89 - 2.36)</td>
<td>2.17 (2.00 - 2.31)</td>
<td>0.451</td>
</tr>
<tr>
<td>E/SRe (cm/s²)</td>
<td>41.4 (36.3 - 46.9)</td>
<td>38.6 (32.9 - 41.1)</td>
<td>0.120</td>
</tr>
</tbody>
</table>

(GLS, global longitudinal strain; SRe, global early diastolic strain rate; E, peak early diastolic mitral inflow velocity)
Table 11. Myocardial deformation parameters of the study population 4 days post-delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features (n = 30)</th>
<th>Controls (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS (%)</td>
<td>−21.7 (−22.6 to −20.8)</td>
<td>−23.0 (−23.9 to −21.8)</td>
<td>0.027</td>
</tr>
<tr>
<td>SRe (s⁻¹)</td>
<td>1.94 (1.82 - 2.24)</td>
<td>2.22 (2.06 - 2.67)</td>
<td>0.020</td>
</tr>
<tr>
<td>E/SRe (cm/s²)</td>
<td>40.5 (35.4 - 47.0)</td>
<td>37.6 (33.2 - 39.3)</td>
<td>0.089</td>
</tr>
</tbody>
</table>

(GLS, global longitudinal strain; SRe, global early diastolic strain rate; E, peak early diastolic mitral inflow velocity)

Similarly to traditional parameters of LV systolic and diastolic function, we found no significant differences in novel myocardial deformation parameters in preeclamptic patients with SGA vs. AGA fetuses/neonates.
Figure 8. A representative example of the measurement of global longitudinal strain (GLS) by two-dimensional speckle tracking method from apical long axis (APLAX), 2-chamber (2ch) and 4-chamber (4ch) views with a bull’s-eye summary in a woman with preeclampsia with severe features. The bull-s-eye view provides the peak systolic mid-wall strain values of all individual left ventricular segments and the average of the strain values representing GLS, denoted by an arrow (→). In this example, GLS is decreased (-15.5%).

(GLS, global longitudinal strain; AVC, aortic valve closure)
Figure 9. A representative example of the measurement of longitudinal peak early diastolic strain rate (SRe) by two-dimensional speckle tracking method from apical long axis (APLAW), 2-chamber (2ch) and 4-chamber (4ch) views in a control subject. SRe is measured from the strain rate curves of each LV segment (peak values are denoted by white dots) and the values are averaged to obtain the global SRe.

**Lung ultrasound**

ECS was significantly higher in women with severe preeclampsia than in controls, both before delivery (p < 0.001) and 1 day post-delivery (p = 0.007); however, this difference was not present 4 days post-delivery (p = 0.091) (Figure 10).

Figure 10 shows ECS in preeclamptic patients compared with controls before delivery and 1 day as well as 4 days post-delivery. Significant changes of ECS over time were observed in preeclamptic group (p = 0.01, ANOVA). ECS values were significantly lower before delivery vs. 1 day post-delivery (p = 0.001) and there was a significant decrease in ECS between days 1 and 4 post-delivery (p = 0.001). Significant difference in ECS over time was also detected in control group (p = 0.02, ANOVA); and post hoc test
revealed that there was a significant increase in ECS at day 1 post-delivery and subsequent decrease at day 4 post-delivery.

Figure 10. Comparison of echo comet score (ECS) values in preeclamptic and control groups. ECS was higher in preeclamptic patients before delivery (p < 0.001), 1 day post-delivery (p = 0.007), but not 4 days post-delivery (p = 0.091). Changes in ECS over time were significant in both groups (p = 0.01 for preeclampsia and p = 0.02 for controls); * represents statistical significance. Data are presented with box-whisker plots with median and interquartile range and minimum and maximum data points.

Figure 11 presents lung ultrasound images before and post-delivery in a study woman with preeclampsia with severe features, showing the lung ultrasound pattern corresponding to extravascular lung water.
Figure 11. Lung ultrasound images in a woman with preeclampsia with severe features before delivery (a) and 1 day (b) and 4 days (c) post-delivery, showing B-lines. Note a decrease in the number of B-lines or comet tails (*), illustrating a progressive decrease in extravascular lung water following delivery.

Significant positive correlations between ECS and diastolic echocardiographic parameters were found; the strongest correlation was observed when ECS was compared with the E/e’ ratio (before delivery: $r = 0.457$, $p < 0.001$; 1 day post-delivery: $r = 0.401$, $p = 0.003$). However, the correlations were more pronounced when only preeclamptic group was analyzed (correlation between ECS and the E/e’ ratio in preeclamptic group before delivery: $r = 0.572$, $p = 0.001$ (Figure 12); 1 day post-delivery: $r = 0.442$, $p = 0.018$ (Figure 13)).
Figure 12. Correlation between E/e’ ratio and echo comet score in preeclamptic patients before delivery.

(E/e’, ratio of the E and average of the septal and lateral e’ velocities)
Figure 13. Correlation between E/e’ ratio and echo comet score in preeclamptic patients 1 day post-delivery.

(E/e’, ratio of the E and average of the septal and lateral e’ velocities)

**Fluid responsiveness**

Results of the PLR are presented in Table 12. There was significantly greater increase in stroke volume with PLR in the control group compared with preeclamptic group before delivery (p = 0.004), but not 1 day post-delivery. We observed a ΔSV of ≥ 12%, indicating fluid responsiveness in significantly more controls (n = 12; 43%) compared to preeclamptic women (n = 3; 11%) (p = 0.014) before delivery. The proportion of fluid responders in both groups was not significantly different 1 day post-delivery.
Table 12. Fluid responsiveness data of the study population before and 1 day post-delivery. Data are given as median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preeclampsia with severe features</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSV (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- before</td>
<td>1.8 (−1.5 - 7.7)</td>
<td>7.9 (2.7 - 20.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>- 1 day post-delivery</td>
<td>5.7 (−0.6 - 11.6)</td>
<td>4.1 (−1.8 - 8.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Fluid responders (n/n of participants, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- before</td>
<td>3/27 (11)</td>
<td>12/28 (43)</td>
<td>0.014</td>
</tr>
<tr>
<td>- 1 day post-delivery</td>
<td>4/27 (15)</td>
<td>2/21 (6)</td>
<td>0.683</td>
</tr>
</tbody>
</table>

(ΔSV, the percent change in stroke volume measured from baseline to passive leg raising)

DISCUSSION

The main findings of the present work can be summarized as follows: a) preeclampsia with severe features is associated with impaired LV diastolic function parameters before delivery and in the first days post-delivery compared with healthy controls; b) preeclampsia with severe features is associated with higher degree of lung congestion before and immediately post-delivery compared with healthy controls; additionally, lung congestion is related to impaired parameters of diastolic function; c) only a small proportion of women with preeclampsia with severe features in our study cohort was fluid responsive.

Hemodynamic and geometric changes

Our data showed significantly higher peripheral vascular resistance and stroke work in preeclamptic women compared with control subjects. These results are consistent with previous hemodynamic studies, which demonstrated high peripheral vascular resistance and low cardiac output in preeclamptic patients. In a subgroup of women with SGA fetuses/neonates, no differences in stroke work nor peripheral vascular resistance were
observed before and 1 day post-delivery. However, 4 days post-delivery we found significantly higher peripheral vascular resistance and lower cardiac output in the SGA compared to AGA group. This finding seems to corroborate the hypothesis of different hemodynamic patterns in preeclampsia and that the higher peripheral vascular resistance in preeclampsia is associated with fetal growth restriction. Similar hemodynamic profile in SGA and AGA groups at the time of delivery and immediately following delivery may be explained by the small number of SGA cases included, definition of SGA by itself and treatment with magnesium sulfate, which could affect echocardiographic parameters. It has to be noted that we analyzed SGA neonatal weight, which is not synonymous with fetal growth restriction. The latter with all its negative effects can be present even in AGA fetuses and is only diagnosed by serial exams showing growth restriction or “crossing the centiles” for gestational age. On the other hand, there are many SGA fetuses, whose small weight is not the consequence of placental dysfunction but their constitution or genetic growth potential. Our results on hemodynamic profiles in preeclampsia with vs. without SGA should not be overinterpreted. They do, however, generate a hypothesis that the high peripheral vascular resistance profile observed in preeclampsia with SGA becomes more pronounced in the first days following delivery. Related to previous studies early-onset preeclampsia and SGA/fetal growth restriction seem to be indicators of the more severe form of the disease. Furthermore, our findings indicate that altered hemodynamic status may persist in women with more severe forms of preeclampsia even days post-delivery. This could be clinically important as it could guide management of preeclamptic patients in the postpartum period. Further studies involving serial hemodynamic measurements in postpartum patients with preeclampsia should be performed to confirm or refute these findings of our study.

We observed slightly but significantly thicker IVS and INFLAT wall and higher LV mass in women with preeclampsia than in controls, possibly reflecting an adaptive remodeling response to increased altered loading conditions. In preeclamptic group higher number of women showed LV remodeling compared with control group. Nevertheless, as preeclampsia with severe features appears as a short time pressure overload, it could therefore not induce remarkable geometric changes in LV mass and geometry.

Similar to other studies, we also found significantly larger left atrial volumes in preeclamptic women compared to control group. However, left atrial remodeling
could not only be the result of increased preload, but also of impaired diastolic function parameters, which was revealed in preeclamptic group.

Left ventricular systolic and diastolic function

The results of our study demonstrated that systolic and diastolic parameters significantly differ between preeclamptic and control group. LV systolic function assessed by conventional echocardiographic parameters (ejection fraction, MAPSE and peak systolic myocardial velocity) did not differ between our study groups immediately before and post-delivery, while 4 days post-delivery we noted significantly lower peak systolic myocardial velocities in women with preeclampsia than in controls, that may suggest subtle impairment of systolic function.

Previous studies on LV systolic function in preeclamptic women assessed by ejection fraction and/or fractional shortening have produced conflicting results. However, most of the data have shown reduced peak systolic Tissue Doppler myocardial velocity and concluded that myocardial contractility in preeclampsia is impaired. None of the studies so far have explored serial changes of systolic function parameters before and immediately after delivery, making the comparison with our results difficult.

In the current work we assessed LV function also with novel myocardial deformation imaging. This promising technique enables an early detection of subtle myocardial functional changes and has been proved to be reproducible and feasible even in clinical use, although measurements vary among vendors and software versions. In our study cohort the median GLS values ± interquartile range were within normal limits proposed by the used vendor. Previously, several authors demonstrated impaired longitudinal strains with values below the normal range, despite of preserved ejection fraction in preeclamptic patients before delivery and also months postpartum. Discrepancies between our and previous data regarding strain parameters could be due to the differences in preeclamptic population with non-uniform hemodynamic pattern (as described above), variable loading conditions and different treatment regime. All women in our preeclamptic group were receiving magnesium sulfate before and 1 day post-delivery, while none of previous studies reported magnesium sulfate treatment at the time.
of echocardiographic examinations. It has been demonstrated that magnesium sulfate may cause sustained reduction in peripheral vascular resistance and an increase in cardiac index in patients with preeclampsia; hence may have an impact on echocardiographic parameters\textsuperscript{40}.

Furthermore, in the studies so far different methods for strain measurements (doppler-derived vs. speckle tracking) and different vendors and software for strain analysis were used that yield variable results and cannot be comparable\textsuperscript{60,62,97}. Additional factors that should be considered when interpreting the results are small number of patients in our study, relatively small differences in strain values and technical limitations of strain imaging which is highly sensitive to image quality.

However, we found significantly lower GLS values in preeclamptic women than in controls 4 days post-delivery, but not before and 1 day post-delivery. These results are in line with previously mentioned results of peak systolic Tissue Doppler velocity, where difference was detected also only 4 days post-delivery.

As both tissue Doppler and myocardial deformation parameters are very sensitive to loading conditions\textsuperscript{98}, loading changes should also be considered when these measurements are interpreted. From previous obstetrics studies, it is known that fluid mobilization from extravascular space occurs after delivery\textsuperscript{21,22}. This physiological phenomenon leads to increased volume load and consequently should augment myocardial contraction, according to the Frank-Starling force-length mechanism, as long as the contractility is normal\textsuperscript{89,99}. Decrease of deformation and peak systolic Tissue Doppler parameters with volume overload after delivery in our preeclamptic women could be explained by assuming that the heart already works on the flat or even descending portion of the Frank-Starling curve at the time of delivery and immediately postpartum; therefore force-length relationship would no longer operate effectively. This observation could indicate that volume overload after delivery might uncover subtle systolic dysfunction in preeclamptic women. An increase in preload would otherwise increase GLS values in fluid responsive subjects as demonstrated in a recent study of critically ill patients\textsuperscript{100}. Our results of passive leg raising test showed that the majority of preeclamptic women were fluid non-responsive before and immediately after delivery. This again indicated that the heart works on the flat portion of the Frank-Starling curve, not able to increase the contraction force with fluid loading.
In contrast to subtle changes of systolic dysfunction, the differences in diastolic parameters were more pronounced in our study population. This is not surprising, as parameters indicating diastolic dysfunction precede systolic impairment in most cardiac diseases and also have important prognostic value.\textsuperscript{101,102,103} While early diastolic mitral inflow velocity E is determined by LV relaxation, filling pressures and volume load, e’ is mainly a measure of myocardial intrinsic properties and reflects myocardial relaxation, relatively less affected by preload. Thus, the E/e’ ratio turns out to be proportional to the LV filling pressures and as such the E/e’ ratio has become clinically widely-used echocardiographic estimate of filling pressures.\textsuperscript{30,31,77,78,104,105} Although the majority of studies have shown a close correlation of the E/e’ ratio with LV filling pressures and its prediction is most reliable when the ratio is < 8 or > 15, there is a broad range of values in healthy people and an overlap of values with cardiac patients, which limit the diagnostic accuracy of the E/e’ ratio particularly in normal healthy subjects.\textsuperscript{104} Namely, in the presence of normal or enhanced LV relaxation, e’ has been shown to be related not only to LV relaxation, but also to preload, contractile state and restoring forces through end systolic volume.\textsuperscript{106-108}

In our study, e’ velocities were lower and E/e’ ratios higher in preeclamptic than in control group, that might suggest impaired LV relaxation and higher LV filling pressures in preeclamptic women. These changes were observed before delivery and also in the first days post-delivery. Lower values were evident for both septal and lateral myocardial velocities; the later were suggested to be less influenced by preload.\textsuperscript{109} It should be noted, however, that in our study cohort the E/e’ ratios were within normal or intermediate reference range according to the guidelines and in only six (20%) preeclamptic cases the ratios were above estimated reference values for elevated LV filling pressure (E/e’\textsubscript{med} > 15, E/e’\textsubscript{lat} > 13 and E/e’ > 14)\textsuperscript{104}. Women with preeclampsia differed also in other Doppler diastolic parameters; the differences were small but reached significance at certain assessments and could be indicative of an early LV diastolic impairment. Other authors reported similar data of disturbed diastolic parameters in women with preeclampsia.\textsuperscript{53,59,60,67,69} In addition to standard diastolic function parameters, we also calculated the e’/s’ ratio, which was proposed as an earlier parameter of impaired myocardial relaxation in intensive care unit patients.\textsuperscript{93} Reduced ratio may reflect abnormal myocardial relaxation compared to preserved systolic function in states of hyperdynamic circulation with presumably low filling pressures. As normal pregnancy is
associated with hyperdynamic circulation and increased stroke work, the e'/s’ ratio may be of value in identifying concealed myocardial impairment in pathological conditions. No studies have evaluated this parameter in pregnancy so far. Our results demonstrated lower e'/s’ ratios in women with preeclampsia than in controls that reached statistically significance 1 day and 4 days post-delivery, further confirming evidence of impaired diastolic function compared with healthy women.

Myocardial deformation imaging can be also used in assessment of diastolic LV function; early diastolic strain rate (SRe) reflects myocardial lengthening and untwisting rate which is coupled to diastolic restoring forces and suction. In a recent study on healthy subjects and patients at risk for diastolic dysfunction with preserved ejection fraction SRe seemed to better detect diastolic function alterations compared with traditional diastolic parameters. Using SRe instead of tissue Doppler e’, which is limited to basal segments and is angle dependent, the E/SRe ratio has been shown to better predict LV filling pressure and prognosis in cardiac disease. In our study we found lower SRe values and higher E/SRe ratios in preeclamptic women compared with controls with significant differences at certain assessments, which confirm evidence of impaired diastolic function, albeit cannot demonstrate additional diagnostic value over traditional diastolic parameters.

Therefore, we could confirm that parameters of LV diastolic function were impaired among women with severe preeclampsia and persisted also in the first days after delivery. We speculate that deterioration of systolic function parameters peak systolic Tissue Doppler velocity and GLS after delivery in preeclamptic women could be related to subtle systolic dysfunction, which becomes unmasked with the effect of augmented volume load related to fluid mobilization in the postpartum period. The augmented volume load could be indicated by our findings of the highest ECS and the E/e’ ratio immediately after delivery.

**Lung ultrasound**

Preeclampsia with severe features was associated with an increase in extravascular lung water before delivery with further increase immediately postpartum. The amount of extravascular lung water then decreased in the first days following delivery, such that at
day 4 postpartum we observed no difference in ECS between preeclamptic women and healthy controls. These findings are in accordance with well-established association of preeclampsia with a higher incidence of pulmonary edema. Furthermore, we found that lung ultrasound can identify increased levels of extravascular lung water in preeclamptic women before clinical signs of pulmonary edema appear; none of the patients included had clinical signs of pulmonary edema despite high ECS values. Therefore, in preeclamptic patients lung ultrasound could help reduce complications associated with fluid over-resuscitation and identify those that would need diuretic therapy.

Additionally, amount of extravascular lung water, assessed by ECS, correlated well with the parameter of LV filling pressure (E/e’ ratio). The correlation was even more pronounced when only preeclamptic group was analyzed. However, increased LV filling pressure could explain only part of the ECS changes as previous studies demonstrated that the mechanism of pulmonary edema in preeclamptic women is associated with increased vascular permeability related to endothelial dysfunction as well as changes in intravascular hydrostatic and plasma oncotic pressure.

Fluid responsiveness

Echocardiographic assessment of fluid responsiveness by PLR could be used to identify women with preeclampsia who will respond to fluids by increasing their cardiac output. Such patients will benefit from further fluid administration when their cardiac output is inadequate to meet their metabolic demands. Based on our results, only a small proportion of women with severe preeclampsia were fluid responsive (before delivery 11% preeclamptic women versus 43% healthy controls, p = 0.014). Our findings are, however, in accordance with the impedance cardiography data, which showed 4 - 15% of pregnant women to be fluid responsive. Brun, et al. found a higher (52%) proportion of fluid responsiveness in severe preeclampsia complicated by oliguria, which highlights the importance of basing fluid therapy and an accurate assessment of the maternal hemodynamic profile.
**Clinical application**

The present work emphasizes that evaluation of lung congestion and cardiac function can be an important part in the management of preeclampsia with severe features allowing to identify women at higher risk of life-threatening complications. Clinical examination alone cannot discriminate between the different hemodynamic patterns in severe preeclampsia. Simple and easy-to-use echocardiographic parameters in combination with lung ultrasound, can be used for assessing fluid responsiveness and fluid tolerance. Firstly, lung ultrasound seems a promising method for identifying women with severe preeclampsia in whom positive fluid balance should be avoided, as it may lead to pulmonary edema. Secondly, echocardiography could help clinicians to identify patients with severe preeclampsia who are still fluid responsive and in whom further fluid administration could be beneficial and the opposite: a patient with an echocardiographic evidence of elevated LV filling pressure is at increased risk for pulmonary edema. Lung ultrasound is relatively quick to learn and following appropriate training anesthesiologists and obstetricians could utilize it as a point-of-care investigation in obstetric complications.

**Strengths and limitations of our study**

To our knowledge this is the first study to serially analyze and demonstrate dynamic changes in extravascular lung water and LV function in women with severe preeclampsia before delivery and in the first days post-delivery. Our observations suggest that recovery of hemodynamic changes in preeclampsia may be prolonged, exposing women to increased risk for cardiac decompensation and pulmonary edema for several days after delivery. Apart from traditional Doppler imaging we included in our study myocardial deformation, that is a promising echocardiographic modality with already proven clinical applications in several cardiac diseases. Diastolic strain rate has not been evaluated in preeclamptic population so far.

The limitations of our study are inherent to the small study population. We intended to focus only on patients with severe features of preeclampsia, as these are critically ill pregnant women who need an accurate assessment of their hemodynamics for good
clinical management. Unfortunately, there can be no optimal controls in these types of study owing to the specific characteristics of preeclamptic patients. Gestational age is known to be an important determinant of hemodynamic status in pregnancy. However, to match controls by gestational age, we would have to have included either patients with spontaneous preterm labor or those with medically indicated preterm delivery. In the first case, maternal hemodynamics would be influenced by labor itself and its possible infectious etiology. In the second case, medically indicated preterm delivery is most often performed, if not for hypertensive disorders of pregnancy, for fetal intrauterine growth restriction. This is most often due to placental malfunction, which again makes such patients non-optimal controls.

In our study we did not analyze diastolic function by the evidence-based algorithms with integration of several diastolic function parameters, therefore we cannot draw firm conclusions on diastolic function and LV filling pressures in our study population. The majority of participants had none or trivial color Doppler signal of tricuspid regurgitation, therefore assessment of peak tricuspid regurgitation velocity was not feasible. Nevertheless, pulsed Doppler and Tissue Doppler velocities and the E/e’ ratios are simple and reproducible echocardiographic parameters that in spite of known limitations are most frequently used in clinical practice. Strain rate imaging, however, has several technical limitations and at present cannot be used in daily clinical practice.

Assessing ECS with the 28-rib interspaces technique is time consuming. Further studies are needed to evaluate simplified techniques, such as the eight anterior regions method, which could be more suitable for everyday clinical practice. All ultrasound examinations and offline analysis were performed by a single investigator, thus avoiding inter-observer variability. Further studies will also be needed to assess reproducibility (i.e. intra-observer and inter-observer variability) of the measurements analyzed. Limitation of our study is also the lack of follow-up data when post-delivery hemodynamic and geometric parameters return to baseline values. Further studies are needed to better understand the pathophysiological effect of preeclampsia on cardiovascular system.
CONCLUSION

Women with preeclampsia with severe features have greater amount of extravascular lung water immediately before and after delivery that could be in part caused by impaired LV diastolic function; therefore, optimal fluid balance is crucial to avoid complications in this vulnerable period. Only a small proportion of preeclamptic women are fluid responsive. In the first days after delivery extravascular lung water in preeclamptic women decreases, while diastolic function parameters are persistently impaired. After delivery myocardial deformation and systolic tissue Doppler parameters slightly decrease, which might reveal subtle systolic dysfunction, uncovered with the effect of augmented volume load related to fluid mobilization in the postpartum period. Our study confirms previous findings of subtle cardiac dysfunction in women with severe features of preeclampsia and provides extended cardiac and lung ultrasound data on serial dynamic changes before and in the first days after delivery. Cardiac ultrasound can be efficiently used as a non-invasive bedside technique for better management of preeclamptic patients.
Uvod

Preeklampsija je ena izmed oblik hipertenzivne bolezni v nosečnosti, ki prizadene približno 2 do 3 % nosečnic v Sloveniji (podatki Nacionalnega perinatalnega informacijskega sistema - NPIS). O težki preeklampsiji govorimo, kadar je povišanemu krvnemu tlaku in proteinuriji pridružena prizadetost enega ali več organskih sistemov 1-3 (Tabela 2). V Sloveniji je bila v zadnjih desetletjih težka preeklampsija drugi najpogostejši vzrok za maternalno umrljivost (podatki Nacionalnega perinatalnega informacijskega sistema - NPIS) (Slika 1).

Dosedanje raziskave hemodinamičnih sprememb pri preeklampsiji so dale različne rezultate, kar je posledica neenakosti med skupinami preiskovank, različnih preiskovalnih metod in tudi vpliva spremenljivih pogojev predobremenitve in poobremenitve srca na hemodinamične kazalce. Pri bolnicah s preeklampsijo so v raziskavah ugotovili dva hemodinamična vzorca: velik minutni volumen srca in nizka periferna žilna uporost ter majhen minutni volumen srca in visoka periferna žilna upornost 37,39,42. Slednji kaže na hujšo obliko bolezni in je bil pogosteje prisoten pri zgodnji preeklampsiji 38,42,44,55,57. Novejše raziskave kažejo, da sta nizek minutni volumen srca in visoka periferna žilna upornost povezana z zastojem rasti ploda, ki se sicer pogosteje pojavlja pri zgodnji preeklampsiji 45. Dosedanje ultrazvočne raziskave so pokazale spremembe kazalcev sistolične in diastolične funkcije pri nekaterih bolnicah s preeklampsijo, vendar rezultati niso povsem primerljivi zaradi različnih skupin preiskovank in različne metodologije 28,57,59,60,63,69.

Eden od življenje ogrožajočih zapletov težke preeklampsije je pljučni edem 1. Domnevajo, da je v nastanek pljučnega edema vpletene več patofizioloških mehanizmov: povečana prepustnost kapilar ob endotelni disfunkciji, povečana periferna žilna upornost, zmanjšano ledvično delovanje, diastolična disfunkcija levega prekata in povečan venski priliv zaradi premika zunajcelične tekočine v žilni prostor v poporodnem obdobju 5,51. Z nadomeščanjem tekočine, s katerim preprečujemo okvaro organov zaradi zmanjšane prekrvavitve, lahko zato pri bolnicah s težko preeklampsijo povečamo
tveganje za nastanek pljučnega edema. Za lažje vodenje in usmerjanje terapije pred in neposredno po porodu pri bolnicah s težko preeklampsijo je zelo koristna neinvazivna ocena hemodinamičnega stanja in srčne funkcije, ki jo omogoča ultrazvočna preiskava. Z ultrazvočnim pregledom srca lahko ocenimo hemodinamične kazalce, srčno funkcijo in odzivnost na tekočino, z ultrazvočnim pregledom pljuč pa stopnjo pljučne kongestije (zunajžilne tekočine v pljučih).

Uporabnost ultrazvočne preiskave pri nosečnicah s težko preeklampsijo je še slabo raziskana, prav tako nimamo podatkov kakšne so dinamične spremembe hemodinamičnih kazalcev in kazalcev srčne funkcije pred in v prvih dneh po porodu.

Namen dela

Namen raziskave je opredeliti uporabnost ultrazvočne preiskave srca in pljuč za oceno hemodinamičnega stanja, srčne funkcije in pljučne kongestije bolnic s težko preeklampsijo pred in v prvih dneh po porodu.

Hipoteze

1. Bolnice s težko preeklampsijo imajo pogosteje prisotne kazalce motene diastolične funkcije levega prekata pred in po porodu v primerjavi z zdravimi nosečnicami.
2. Bolnice s težko preeklampsijo imajo večjo stopnjo pljučne kongestije pred in po porodu v primerjavi z zdravimi nosečnicami.
3. Bolnice s težko preeklampsijo so manj odzivne na tekočino v primerjavi z zdravimi nosečnicami.
4. Stopnja pljučne kongestije je povezana s kazalci diastolične disfunkcije.
Zasnova raziskave, opis preiskovank in metod

Preiskovanke


Zasnova raziskave

Preiskovankam v skupini s težko preeklampsijo in v kontrolni skupini smo opravili ultrazvočno preiskavo srca in pljuč dan pred porodom, dan po porodu in četrti dan po porodu. Ob vsakem pregledu smo izmerili krvni tlak z avtomatičnim oscilometričnim merilcem krvnega tlaka. Odzivnost na tekočino smo ocenili dan pred in dan po porodu (Slika 4).

Ultrazvočna preiskava srca in pljuč


Preiskovankam smo opravili standardno transtorakalno ultrazvočno preiskavo srca po evropskih in ameriških priporočilih. Izmerili smo srčne dimenzije in debelino sten levega prekata, izračunali maso levega prekata in hemodinamične kazalce ter ocenili sistolično in diastolično srčno funkcijo s klasičnimi dvodimenzionalnimi, doplerskimi in tkivno doplerskimi metodami. V raziskavo smo vključili tudi meritve deformacije miokarda levega prekata z uporabo metode sledenja ultrazvočnega vzorca (ang. speckle tracking imaging). S to metodo smo ocenili globalni kazalec deformacije levega prekata v longitudinalni smeri (angl. global longitudinal strain - GLS), ki velja za občutljivejši kazalec okvare sistolične funkcije v primerjavi z iztisnim deležem levega prekata in.
zgodnjo diastolično hitrost deformacije miokarda (angl. global early diastolic strain rate - SRe), ki je novejši kazalec diastolične funkcije levega prekata \(^{91,111}\).

Ultrazvočni pregled pljuč smo opravili v ležečem položaju po protokolu 28 medrebrnih prostorov (Slika 5). Na osnovi prisotnosti in števila B linij smo ocenili stopnjo pljučne kongestije; vsota B linij v 28 medrebrnih prostorih je predstavljala količino zunajžilne pljučne tekočine (Echo Comet Score - ECS) \(^{75,76}\).

**Odzivnost na tekočino**

Odzivnost na tekočino smo opredelili s spremembo utripnega volumna, ocenjenega s pulzno doplersko preiskavo ob pasivnem dvigu nog \(^{85,87}\). Odzivnost na tekočino smo definirali kot povečanje utripnega volumna za \(\geq 12\%\) \(^{94}\).

**Statistične metode**

Podatke smo statistično obdelali s programom SPSS 21.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Meritve dan pred porodom, prvi dan po porodu in četrti dan po porodu smo v skupini preeklamptičnih bolnic in v kontrolni skupini primerjali z Mann Whitney U-testom pri zveznih spremenljivkah in s Hi-kvadrat ali Fisherjevim testom pri kategoričnih spremenljivkah. Razlike spremenljivk znotraj posamezne skupine pred porodom, prvi dan po porodu in četrti dan po porodu smo ovrednotili z analizo variance (angl. ANOVA). Spearmanov koefficient korelacije smo uporabili za analizo povezanosti ECS in kazalcev diastolične funkcije levega prekata. Pri vseh testih smo kot statistično značilne upoštevali tiste razlike, pri katerih je bila vrednost \(p < 0,05\).

**Rezultati**

**Klinične značilnosti preiskovank**

Med skupinama ni bilo statistično značilnih razlik v starosti, indeksu telesne mase pred nosečnostjo in ob vključitvi v raziskavo. Skupina s preeklampsijo je imela nižjo gestacijsko starost in več prvorodnic v primerjavi s skupino zdravih nosečnic (\(p < 0,001\)) (Tabela 3).
**Hemodinamične značilnosti**

Preeklamptične bolnice so imele pričakovano višji sistolični, diastolični in srednji krvni tlak ter višjo periferno žilno upornost v primerjavi s kontrolno skupino (p ≤ 0,001). Med skupinama ni bilo statistično značilnih razlik v srčni frekvenci, utripnem in minutnem volumnu srca (Tabela 4).

**Geometrični kazalci srca**

Preeklamptične bolnice so imele debelejši prekatni pretin (p = 0,036) in inferolateralno steno (p = 0,043) ter večjo maso levega prekata (p < 0,001) v primerjavi z zdravimi nosečnicami. Med skupinama ni bilo razlik v relativni debelini sten, dimenzijah in indeksu sferičnosti levega prekata. Večji delež preoblikovanega levega prekata smo ugotovili v skupini preeklamptičnih nosečnic (p = 0,028). Volumen levega preddvora je bil statistično značilno večji v skupini nosečnic s težko preeklampsijo (p < 0,001) (Tabela 5).

**Sistolična in diastolična funkcija levega prekata**

Preeklamptične bolnice so imele značilno nižje vrednosti najvišje sistolične hitrosti miokarda (s') v primerjavi s kontrolno skupino četrti dan po porodu (s' na medialnem mitralnem obroču: p = 0,001 in s' na lateralnem mitralnem obroču: p = 0,040), nismo pa našli razlik v iztisnem deležu levega prekata in longitudinalnem gibanju mitralnega obroča (angl. mitral annular plane systolic excursion - MAPSE) (Tabele 6-8). Preeklamptične bolnice so imele tudi značilno nižje vrednosti GLS četrti dan po porodu v primerjavi s kontrolno skupino (p = 0,027) (Tabele 9-11).

V skupini bolnic s težko preeklampsijo in v skupini zdravih nosečnic ni bilo razlik v iztisnem deležu levega prekata in GLS med meritvami pred porodom, prvi dan po porodu in četrти dan po porodu.

Med skupinama smo ugotovili razlike v kazalcih diastolične funkcije levega prekata. Vrednosti zgodnje diastolične hitrosti miokarda (e') na septalnem in lateralnem mitralnem obroču so bile značilno nižje (p < 0,001), razmerje zgodnje diastolične hitrosti mitralnega vtoka E in e' (E/e') pa značilno večje v skupini s preeklampsijo v primerjavi s kontrolno skupino pred porodom, prvi dan po porodu in četrtri dan po porodu (p < 0,001) (Tabele 6-8).
V skupini s preeklampsijo so bile med posameznimi preiskavami pomembne spremembe razmerja E/e' (p = 0,02, ANOVA): razmerje E/e' je bilo pomembno večje prvi dan po porodu v primerjavi z razmerjem pred porodom (p = 0,001) in četrti dan po porodu (p = 0,001) (Slika 6).

Pri preeklamptičnih bolnicah smo našli tudi značilno nižje vrednosti SRe pred porodom (p = 0,015) in četrti dan po porodu (p = 0,020) (Tabele 9-11).

Pljučna kongestija

Seštevek B-linij je bil večji v skupini s preeklampsijo v primerjavi s kontrolno skupino pred porodom (p < 0,001) in prvi dan po porodu (p = 0,007), ni pa se pomembno razlikoval štiri dni po porodu (Slika 10). V skupini s preeklampsijo smo ugotovili pomembne spremembe v ECS (p = 0,01, ANOVA): ECS je bil nižji pred porodom v primerjavi z ECS prvi dan po porodu (p = 0,001) in znova nižji četrti dan po porodu (p = 0,001). Podobne spremembe v ECS smo našli tudi v kontrolni skupini (p = 0,02, ANOVA): povečanje ECS prvi dan po porodu in nato znižanje četrti dan po porodu (Slika 10).

Dokazali smo tudi pomembno povezavo med ECS in E/e’ v skupini s preeklampsijo pred porodom (r = 0,572, p = 0,001) in prvi dan po porodu (r = 0,442, p = 0,018) (Slika 12, 13).

Odzivnost na tekočino

Pred porodom je bilo več zdravih nosečnic odzivnih na tekočino (12; 43%) v primerjavi s preeklamptičnimi bolnicami (3; 11%) (p = 0,014). Dan po porodu med skupinama ni bilo razlik v odzivnosti na tekočino (Tabela 12).

Zaključki

1. Pri bolnicah s težko preeklampsijo so pogosteje prisotni kazalci motene diastolične funkcije levega prekata pred porodom in v prvih dneh po porodu v primerjavi z zdravimi nosečnicami. Po porodu se pri preeklamptičnih bolnicah vrednosti s' in GLS zmanjšajo, kar lahko kaže tudi na subtilno okvaro sistolične
funkcije, ki se razkrije ob povečani volumski obremenitvi srca zaradi premika tekočine iz zunajžilnega prostora.

2. Bolnice s težko preeklampsijo imajo večjo stopnjo pljučne kongestije pred in po porodu v primerjavi z zdravimi nosečnicami. Stopnja pljučne kongestije je povezana s kazalci diastolične disfunkcije. V prvih dneh po porodu se pri preeklamptičnih bolnicah stopnja pljučne kongestije zmanjša, medtem ko kazalci motene diastolične funkcije vztrajajo.

3. V naši raziskavi je bila večina bolnic s težko preeklampsijo neodzivna na tekočino.
Tables and figures

List of tables

Table 1. Diagnostic criteria for preeclampsia 16
Table 2. Diagnostic criteria for preeclampsia with severe features (any of the following) 17
Table 3. Study population characteristics 36
Table 4. Hemodynamic characteristics of the study population before delivery 38
Table 5. Cardiac dimensions of the study population before delivery 40
Table 6. Left ventricular systolic and diastolic function parameters of the study population before delivery 43
Table 7. Left ventricular systolic and diastolic function parameters of the study population 1 day post-delivery 44
Table 8. Left ventricular systolic and diastolic function parameters of the study population 4 days post-delivery 45
Table 9. Myocardial deformation parameters of the study population before delivery 48
Table 10. Myocardial deformation parameters of the study population 1 day post-delivery 48
Table 11. Myocardial deformation parameters of the study population 4 days post-delivery 49
Table 12. Fluid responsiveness data of the study population before and 1 day post-delivery 56

List of figures

Figure 1. Maternal deaths in Slovenia in 2000-2014, Slovenian Institute for Public Health 18
Figure 2. Preeclampsia as a cause of very preterm birth (< completed 32 weeks of gestation) in 2003-2012, National Perinatal Information System data for Ljubljana Maternity Hospital 19
Figure 3. Hemodynamic changes in pregnancy, during labor and postpartum 21
Figure 4. Study protocol 30
Figure 5. Distribution and the serial numbers of the 28-rib interspaces on the chest wall for assessment of the Echo Comet Score

Figure 6. Comparison of the E/e’ ratios in the severe features of preeclampsia and control groups

Figure 7. A representative example of pulsed wave Doppler (a, c) and tissue Doppler (b, d) curves in a study woman with severe features of preeclampsia (a, b) and a healthy control (c, d)

Figure 8. A representative example of the measurement of global longitudinal strain (GLS) by two-dimensional speckle tracking method from apical long axis (APLAX), 2-chamber (2ch) and 4-chamber (4ch) views with a bull’s-eye summary in a woman with severe features of preeclampsia

Figure 9. A representative example of the measurement of longitudinal peak early diastolic strain rate (SRe) by two-dimensional speckle tracking method from apical long axis (APLAW), 2-chamber (2ch) and 4-chamber (4ch) views in a control subject

Figure 10. Comparison of echo comet score (ECS) values in the severe preeclampsia and control groups

Figure 11. Lung ultrasound images in a woman with severe features of preeclampsia before delivery (a) and 1 day (b) and 4 days (c) post-delivery, showing B-lines

Figure 12. Correlation between E/e’ ratio and echo comet score in preeclamptic patients before delivery

Figure 13. Correlation between E/e’ ratio and echo comet score in preeclamptic patients 1 day post-delivery
REFERENCES


3. Cerar VM. Najnovejša spoznanja o nastanku preeklampsije in njihove posledice v njenem preprečevanju, zgodnjem odkrivanju ter zdravljenju. Recent advances in the pathogenesis of preeclampsia and their implications in prevention, early detection and therapy. In: Takač I, eds. 40 let perinatalne medicine v Sloveniji; 2006; UKC Maribor, Slovenija.


