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Maternal body fluid composition in uncomplicated pregnancies and preeclampsia: a bioelectrical impedance analysis.

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Condensation

Using bio-impedance analysis shows that body fluid composition changes differently during the course of an uncomplicated versus hypertensive pregnancy. Late onset preeclampsia is associated with a higher total body water and extracellular water as compared to uncomplicated pregnancies.

Abstract

Objectives: Body fluid composition changes during the course of pregnancy and there is evidence to suggest that these changes are different in uncomplicated pregnancies compared to hypertensive pregnancies. The aim of this study was to evaluate the changes in maternal body fluid composition during the course of an uncomplicated pregnancy and to assess differences in uncomplicated pregnancies versus hypertensive pregnancies by using a bio-impedance analysis technique.

Study design: Body fluid composition of each patient was assessed using a multiple frequency bioelectrical impedance analyser. Measurements were performed in 276 uncomplicated pregnancies, 34 patients with gestational hypertension, 35 with late onset preeclampsia and 11 with early onset preeclampsia. Statistical analysis was performed at nominal level α=.05. A longitudinal linear mixed model based analysis was performed for longitudinal evolutions, and ANOVA with a post-hoc Bonferroni was used to identify differences between groups.

Results: Measurements showed that total body water (TBW), extracellular water (ECW) and ECW/ICW significantly increase during the course of pregnancy, whereas intracellular water (ICW) does not. Late onset preeclampsia is associated with a higher TBW and ECW as compared to uncomplicated pregnancies, the ECW/ICW ratio is higher in preeclamptic patients compared to uncomplicated pregnancies and gestational hypertension, and ICW is not different between groups.

Conclusion: Body fluid composition changes differently during the course of uncomplicated pregnancies versus hypertensive pregnancies.

Keywords

Pregnancy, body fluid composition, preeclampsia, body fluid, bio impedance analysis

Introduction

During pregnancy, a large proportion of the maternal weight gain is attributed to maternal fluid retention: plasma volume and maternal cardiac output increase, and physiological peripheral oedema is a clinical sign of an accumulation of extra-cellular water (ECW) (1). The symptoms of preeclampsia like plain oedema, hypertension and oliguria suggest that total body water (TBW) is different in preeclamptic patients compared to uncomplicated pregnancies. However, conclusions regarding body composition, and TBW in particular, are still inconsistent in literature (2-4). Nevertheless, changes in TBW as part of the total body composition is of potential interest to clinicians as abnormal fluid adaptation might give rise to maternal and foetal pathologies such as intrauterine growth restriction (5) or hypertensive gestational complications (6).

Fluid changes can be assessed by using a dilution method, although these techniques are expensive and not easy to use (7). Bioelectrical impedance technique is a technique which relies on the conduction of an alternating electrical current to determine the total conductor volume of the body and as such to estimate whole body extra cellular fluid content (8). The technique is safe for both mother and a developing foetus, however studies during pregnancy are scarce.

The aim of this study was 1) to evaluate the changes in maternal body fluid composition during the course of an uncomplicated pregnancy and 2) to assess differences in body fluids in uncomplicated pregnancies versus hypertensive pregnancies by using a bio-impedance analysis (BIA) technique.

Methods

Ethics

Approval of the local ethical committee was obtained before study onset (MEC ZOL 14/002U). Oral and written informed consent was obtained in every patient.

Repeatability of the BIA-measurements

The repeatability of the BIA-measurement was investigated before study-onset. 20 pregnant women were selected on voluntary basis in whom one single BIA-measurement was performed twice a day (AM and PM). Measurements were done in supine position and irrespective of fluid or food intake or daily activity. In a subset of 10 women, to assess repeated versus single measurements, Pearson correlations were calculated between AM and PM sessions and between a single versus 2, 3, 4 or 5 measurements. The latter was performed within a time interval of one minute . One patient was excluded from the analysis as no PM measurements were performed.

Subjects

Women admitted between October 2013 and April 2015 to the Maternal Intensive Care Unit of Ziekenhuis Oost-Limburg (Genk, Belgium) for hypertension in pregnancy were included. Gestational hypertension (GH) was defined as blood pressure ≥140/90 mmHg on 2 occasions at least 6 hours apart, after 20 weeks of gestation, according to the criteria of the National High Blood Pressure Education Program Working Group (9). Preeclampsia (PE) was defined as gestational hypertension with de novo proteinuria (≥300 mg/24 hours) with PE < 34 weeks defined as early onset preeclampsia (EPE), whereas PE ≥ 34 weeks was defined as late onset preeclampsia (LPE). All hypertensive patients had one BIA-measurement, at the time of diagnosis. Patients with essential hypertension, which is defined as hypertension diagnosed before the 20^{th} week of gestation, were excluded. Other exclusion criteria were women with multiple gestation, renal disease, history of organ transplantation, women with liver disease, and women with signs of atypical preeclampsia, such as HELLP syndrome without proteinuria or with non-hypertensive proteinuria.

Women with a normal uncomplicated ongoing pregnancy (UP) were eligible for inclusion in the control group and were effectively included only when normal maternal and neonatal outcome was confirmed after birth. For this group, BIA-measurements were performed at the gestational age according to the protocols of ongoing studies on maternal hemodynamics in Ziekenhuis Oost-Limburg (Genk, Belgium). Study patients were categorised into 4 groups: (1) UP, (2) GH, (3) EPE and (4) LPE. To compare the hypertensive groups with UP excluding gestational age as a possible confounder, a case-control group matching for gestational age was initiated by analysing a subgroup of UP.

For all patients, weight and height at time of measurement and gestational outcome were noted and weight before pregnancy was found in the medical file. Data of a urine collection and blood sample was collected for all hypertensive patients.

Study-design

Body fluid composition of each patient was assessed using a multiple frequency bioelectrical impedance analyser (Maltron Bioscan 920-II®, Maltron International LTD, Essex, UK). 4 electrodes were placed: two on the right hand and two on the right bare foot: the receiving electrodes were attached at the dorsal side of the right wrist and ankle, the sending electrodes were placed at the distal end of the metacarpal and metatarsal bones. The applied current was 0.6 mA which was transmitted in 4 different frequencies (5, 50, 100 and 200 kHz), during 5 seconds. Measurements were performed in supine position after 5 minutes of rest in all patients. Three fluid parameters were recorded: total body water (TBW), which is the sum of extracellular water (ECW) and intracellular water (ICW). Finally, the ratio ECW/ICW was calculated.

Statistics

To analyse the longitudinal evolution over the course of pregnancy, a longitudinal linear mixed model based analysis, which accounts for within-subject repetition (10), was performed in SAS (Version 9.4/13.2) for all measurements of the UP-group. A sufficiently general model was fitted so as to avoid parametric inadequacy. Because inferences are based on the fixed effects in the model only, they are

119 valid even when the data are not entirely normally distributed, by invoking large-sample theory. The
120 time evolution in each of the models can be used to assess the change over time of the fluid
121 parameters.
122 Next, SPSS software version 20.0 was used for statistical comparison at nominal level α=.05. ANOVA
123 with a post-hoc Bonferroni was used to identify differences of fluid parameters and demographical
124 characteristics between groups. Pearson correlations were used to calculate the repeatability of the
125 BIA-measurements.

Results

Repeatability of the BIA-measurements

Pearson correlation between AM and PM session based on one single BIA-measurement was >.84 for all fluid parameters. This correlation did not improve when the mean of multiple measurements was calculated (>.85, >.83, >.79 and >.81 for the mean of two, three, four and five measurements, respectively). From this, single measurements irrespective of time of day, diet or physical activity were used for this study.

Longitudinal evolution of fluid parameters

There is a variable number of repetitions within a patient, resulting in 517 BIA measurements obtained in 276 uncomplicated pregnancies. TBW, ECW and ECW/ICW are shown to increase significantly during the course of UP, which is not true for ICW. Longitudinal evolution is shown in Figure 1.

Demographics

As gestational age influences body fluids (figure 1), BIA-measurements of the UP group in the third trimester (≥ 30 weeks) were selected as a subgroup, with one single measurement for each patient, to compare UP with the hypertensive pregnancies. Demographic characteristics are presented in table 1. Gestational age of UP did not differ from the other groups, except from EPE where patients were included and delivered significantly earlier compared to the other groups ($p<.004$). Maternal weight and BMI was not significant between groups. Compared to UP, foetal birth weight and birth weight centile were lower in the LPE group despite a similar gestational age at delivery ($p\leq.001$). Within the preeclamptic groups, foetal birth weight was higher in LPE as compared to EPE (2789±512 vs 1517±479 for LPE and EPE respectively, $p<.001$), however birth weight centile did not differ significantly. 24-hours proteinuria was highest in patients with EPE ($p<.044$ compared to LPE and GH).

Body fluids in uncomplicated and hypertensive pregnancies

Results are presented in table 2. TBW and ECW were found to be significantly higher in patients with LPE compared to UP, which is not true for EPE and GH. There was no significant difference in TBW

and ECW between the subtypes of hypertensive pregnancies. Next, the ratio ECW/ICW was significantly lower in UP compared to the hypertensive groups ($p<.041$). ECW/ICW was higher in LPE and EPE than in GH ($p=.012$ and .040, respectively), but was not different between preeclampsia groups. These data are plotted in figure 2. Finally, ICW was not different in between groups.

Comment

In this study, we assessed the maternal body fluid composition by using BIA during the course of an uncomplicated pregnancy and in patients diagnosed with different types of gestation induced hypertensive diseases. We found that TBW and ECW increased during the course of normal pregnancy, that LPE is associated with a higher TBW and ECW compared to UP and we observed a higher ECW/ICW ratio in preeclamptic patients.

Our study is original in the multi-frequency analysis aspect of the BIA-technique, which allows true estimating ECW and ICW in the different groups, and obtaining additional information on the gestational body fluids (8). We speculate that of amniotic fluid and the foetus might influence the results when analysing the 'maternal' body fluid composition with BIA, which is a possible limitation of our study. Data regarding serum osmolarity and albumin concentrations are not available, which could be useful to better understand and explain the differences observed between groups. Next, this study fails to observe significant differences between the hypertensive groups, which might perhaps relate to the relatively small amount of subjects in the hypertensive groups. The use of medication in a small fraction of hypertensive groups might have been a potential confounder. Since the conflicting results in different papers, the BIA technique should be validated very carefully in future research.

Longitudinal evolution of fluid parameters

During normal pregnancy, the vascular bed enlarges and the total systemic resistance decreases due to generalized vasodilatation (11). As a consequence, an activated renin-angiotensin-aldosterone system helps retain salt and water in pregnancy since the maternal systemic vasodilatation creates an underfilled cardiovascular system (12). This mechanism of fluid retention maintains blood pressure and results in an increasing cardiac output and blood volume (i.e. plasma volume and blood products). The increasing TBW and ECW during an uncomplicated pregnancy found in this study, is in line with different other studies (4, 13-15). The slight decrease of ECW at earlier gestation till 14 weeks as reported by Larciprete et al. could not be confirmed in our study (14).

The longitudinal evolution of fluid parameters in our study shows a non-significant increase of ICW. This is in contrast with the findings of two papers of the research group of De Lorenzo, in which they reported a moderate but significant increase of ICW during the third trimester (4, 14). They explained a slight increase of ICW at the end of gestation by the water-filling need of the breast tissue and the inferior pelvis in order to guarantee the correct course of labour, delivery and puerperium (14).

Body fluids in uncomplicated and hypertensive pregnancies

We observed that types of gestation induced hypertensive complications are characterized with different phenotypes of maternal body fluid composition: significantly more TBW in LPE compared to patients with UP at a comparable gestational age, which is not true for EPE and GH versus UP (table 2). Reported classification of preeclampsia into an early- and late-onset disease differentiates two distinct clinical forms with pathophysiological specific features, in which EPE is commonly associated with intrauterine growth restriction and adverse maternal and perinatal outcomes, whereas LPE is associated with a milder clinical course (16). As maternal vascular maladaptation in preeclampsia is more pronounced in EPE compared to LPE (17, 18), indicating a more compliant vascular system in LPE versus EPE, and 75% of plasma volume is located in the venous compartment, it can be considered that the higher TBW and ECW observed in LPE is a sign of fluid overload in a rather well adapted venous system (17). This overload may be responsible for retrograde dysfunction of the capillary network, presenting clinically as various degrees of peripheral edema. The lack of an increased TBW and ECW in EPE patients can be interpreted as an inability to store the fluid appropriately due to a non-compliant venous system. The increased ECW/ICW ratio, which is also seen in critically ill patients (8), is found in both LPE and EPE. This study however does not allow conclusions on cause-and-effect relationship: it is unclear whether the aberrant ECW/ICW ratio in preeclampsia is a preexisting condition or triggered by the pregnancy or disease onset. For this, a large prospective clinical trial is needed.

The increased TBW in LPE in this study is in concordance with the report of Levario-Carrillo et al. (6), but inconsistent with the results reported by Valensise et al (4). The latter studied patients with

uncomplicated pregnancies and gestational hypertension and found a significantly lower TBW, ECW and ICW in the hypertensive group (TBW: 17.5±3.4L versus 44.4± 7.2L for UP and GH respectively). They explained it as a reduction in circulating plasma volume as an indicator of maladaptation to pregnancy. Uncomplicated pregnancies are reported with an increase of 50% in plasma volume, while complicated pregnancies are, from early pregnancy onwards, characterized by a much smaller plasma volume increment, this increment probably being lowest in early-onset pre-eclampsia. However, Valensise did not include preeclamptic patients, and used a different method to detect bioelectrical impedance. Next, given that ECW consists of plasma fluid and interstitial fluid and that preeclamptic patients are mostly vascular underfilled while presenting with distinct oedema, low TBW cannot be equated to low plasma volume. The evolution of plasma volume in different types of gestational induced hypertensive diseases and its correlation with TBW, obtained with BIA, is a subject for future research.

In conclusion, this study found that one single measurement is valid to obtain an accurate profile of body fluid during pregnancy. The adaptation of maternal body fluids in the course of pregnancy is different in uncomplicated versus hypertensive pregnancies. This might be interesting in a screening-setting, however future research is needed.

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Conflict of interests

Non to declare

234 **Tables** Table 1 : Demographic characteristics

	UP (n=72)	GH (n=34)	p (to UP)	LPE (n=35)	p (to UP)	EPE (n=11)	p (to UP)
Weight before pregnancy [kg]	70.72±16.76	73.94±16.71	1.00	68.53±18.04	1.00	69.00±12.11	1.00
BMI before pregnancy	25.3±6.1	26.5±5.0	1.00	24.7±5.7	1.00	23.7±9.0	1.00
Weight at inclusion [kg]	83.65±18.35	86.97±17.63	1.00	83.15±16.58	1.00	81.51±12.81	1.00
BMI at inclusion	29.9±6.7	31.3±5.5	1.00	32.0±13.4	1.00	30.9±4.6	1.00
Gestational age at inclusion [weeks]	**35.8±3.5**	**36.7±4.7**	1.00	**37.5±1.8**	.113	31.9±2.6	.004
Gestational age at delivery [weeks]	**39.0±2.4**	**38.6±2.0**	1.00	**38.0±1.5**	.154	32.3±2.5	<.001
Foetal birth weight [g]	**3320±668**	**3119±647**	.721	**2789±512**	<.001	1517±479	<.001
Foetal birth weight centile	**54.1±29.9**	**47.7±31.2**	1.00	29.6±23.8	<.001	19.3±14.6	.001
Hematocrit [%]	/	36.44±2.39	/	35.22±3.16	/	36.71±2.22	/
GOT [ASAT] [U/L]	/	20.16±18.34	/	24.41±27.21	/	20.55±9.54	/
GPT [ALAT] [U/L]	/	17.29±20.79	/	23.50±50.45	/	14.09±6.64	/
Uric acid [mg/dL]	/	5.47±1.60	/	5.84±1.30	/	6.32±1.54	/
Proteinuria [mg/24 hours]	/	**158±72**	**/**	**1343±1666**	/	2709±2984	/
Antihypertensive medication [n (%)]	0 (0%)	6 (17.6%)	<.001	8 (22.8%)	<.001	5 (45.5%)	<.001

235

236 Demographic characteristics of all groups presented as mean ± standard deviation. Differences with UP are reported with a p-value. Significant differences

237 relative to EPE are marked in bold.

238 UP: uncomplicated pregnancy, GH: gestational hypertension, LPE: late onset preeclampsia, EPE: early onset preeclampsia.

Table 2: Fluid status in uncomplicated and hypertensive pregnancies

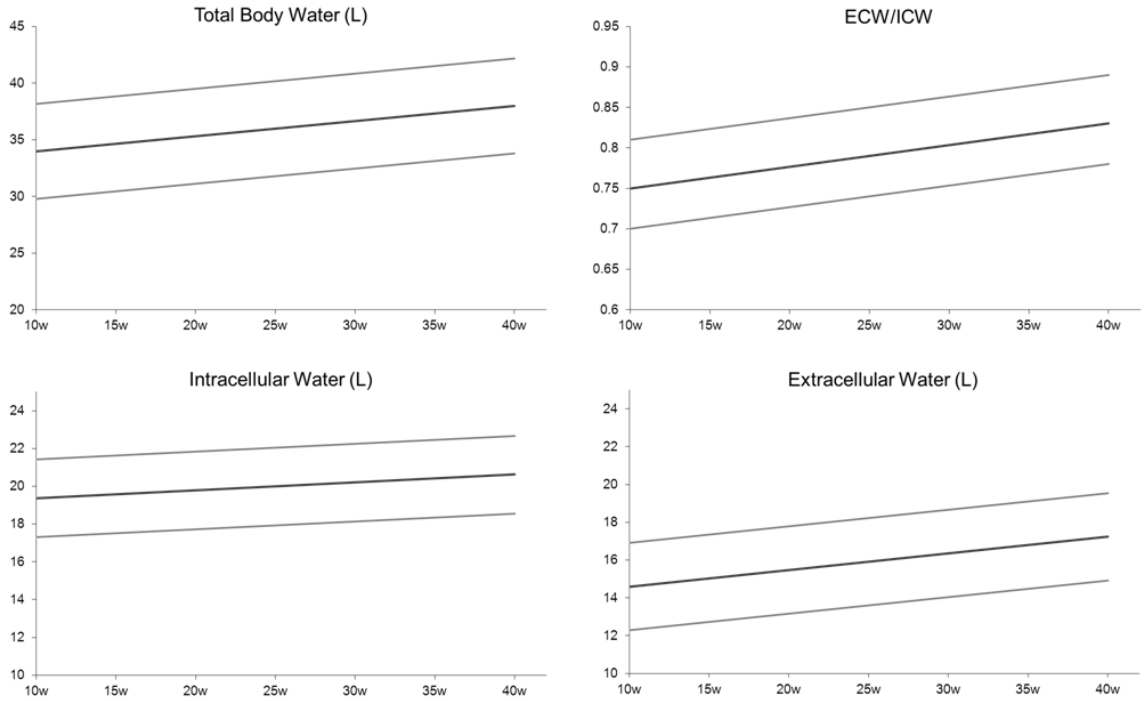
	UP (n=72)	GH (n=34)	p-value	LPE (n=35)	p-value	EPE (n=11)	p-value
TBW	37.58±4.91	39.84±6.14	.330	**41.50±5.84**	**.003**	39.36±3.76	1.00
ECW	16.90±2.84	18.44±3.48	.140	**20.00±3.50**	**<.001**	18.90±2.63	.310
ICW	20.55±2.50	21.40±2.84	.835	21.56±2.57	.336	20.46±1.34	1.00
ECW/ICW	0.815±0.07	**0.860±0.08**	**.041**	**0.922±0.09**	**<.001**	**0.921±0.09**	**<.001**

Data presented as mean ± standard deviation. P-values are reported relative to UP with significance differences marked in bold

TBW: Total Body Water, ECW: extracellular water, ICW: intracellular water, ECW/ICW: ratio between extracellular and intracellular water, UP: uncomplicated pregnancy, GH: gestational hypertension, LPE: late onset preeclampsia, EPE: early onset preeclampsia.

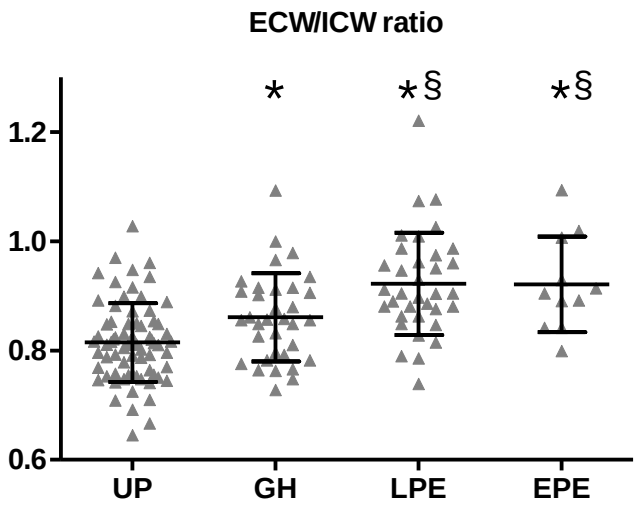
Figures

Figure 1: Longitudinal evolution of fluid status during uncomplicated pregnancies



Data presented as mean with standard deviation. All fluid parameters increases significantly (p<.001). ECW: extracellular water, ICW: intracellular water, ECW/ICW: ratio between extracellular and intracellular water.

Figure 2: The extracellular water/intracellular water ratio



Data presented as scatter plots with mean and standard deviation. Groups significant different from UP are indicated with an asterisk (*), and groups significant different from GH are indicated with §. UP: uncomplicated pregnancies, GH: gestational hypertension; LPE: late-onset preeclampsia; EPE: early-onset preeclampsia.

References

1. Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. Obstet Gynecol Surv 1994;49(12 Suppl):S1-14.
2. Yasuda R, Takeuchi K, Funakoshi T, Maruo T. Bioelectrical impedance analysis in the clinical management of preeclamptic women with edema. J Perinat Med 2003;31(4):275-80.
3. Martin A, O'Sullivan AJ, Brown MA. Body composition and energy metabolism in normotensive and hypertensive pregnancy. BJOG 2001;108(12):1263-71.
4. Valensise H, Andreoli A, Lello S, Magnani F, Romanini C, De Lorenzo A. Multifrequency bioelectrical impedance analysis in women with a normal and hypertensive pregnancy. Am J Clin Nutr 2000;72(3):780-3.
5. Levario-Carrillo M, Rodriguez N, Tufino-Olivares E, Jimenez Mdel R, Delgado-Monge MC, Reza-Lopez S. Body composition of women with newborns who are small for gestational age. Neonatology 2009;95(1):15-22.
6. Levario-Carrillo M, Avitia M, Tufino-Olivares E, Trevizo E, Corral-Terrazas M, Reza-Lopez S. Body composition of patients with hypertensive complications during pregnancy. Hypertens Pregnancy 2006;25(3):259-69.
7. Elia M. Body composition by whole-body bioelectrical impedance and prediction of clinically relevant outcomes: overvalued or underused? Eur J Clin Nutr 2013;67 Suppl 1:S60-70.
8. Malbrain ML, Huygh J, Dabrowski W, De Waele JJ, Staelens A, Wauters J. The use of bio-electrical impedance analysis (BIA) to guide fluid management, resuscitation and deresuscitation in critically ill patients: a bench-to-bedside review. Anaesthesiol Intensive Ther 2014;46(5):381-91.
9. Gifford R, August P, Cunningham G. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183(1):S1-S22.
10. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data (2nd edn). New York: Springer; 2001.
11. Gyselaers W, Mesens T, Tomsin K, Peeters L. Doppler assessment of maternal central venous hemodynamics in uncomplicated pregnancy: a comprehensive review. Facts Views Vis Obgyn 2009;1(3):171-81.
12. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation 2014;130(12):1003-8.
13. Ghezzi F, Franchi M, Balestreri D, et al. Bioelectrical impedance analysis during pregnancy and neonatal birth weight. Eur J Obstet Gynecol Reprod Biol 2001;98(2):171-6.
14. Larciprete G, Valensise H, Vasapollo B, et al. Body composition during normal pregnancy: reference ranges. Acta Diabetol 2003;40 Suppl 1:S225-32.
15. Lukaski HC, Siders WA, Nielsen EJ, Hall CB. Total body water in pregnancy: assessment by using bioelectrical impedance. Am J Clin Nutr 1994;59(3):578-85.
16. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. Circulation 2014;130(8):703-14.
17. Gyselaers W, Mesens T, Tomsin K, Molenberghs G, Peeters L. Maternal renal interlobar vein impedance index is higher in early- than in late-onset pre-eclampsia. Ultrasound Obstet Gynecol 2010;36(1):69-75.
18. Gyselaers W, Staelens A, Mesens T, et al. Maternal venous Doppler characteristics are abnormal in pre-eclampsia but not in gestational hypertension. Ultrasound Obstet Gynecol 2015;45(4):421-6.