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

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14 The reported work was performed in Ziekenhuis Oost-Limburg, Genk, Belgium.

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24 **Condensation**

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

28

29 **Abstract**

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

35 Study design: Body fluid composition of each patient was assessed using a multiple frequency  
36 bioelectrical impedance analyser. Measurements were performed in 276 uncomplicated pregnancies,  
37 34 patients with gestational hypertension, 35 with late onset preeclampsia and 11 with early onset  
38 preeclampsia. Statistical analysis was performed at nominal level  $\alpha=.05$ . A longitudinal linear mixed  
39 model based analysis was performed for longitudinal evolutions, and ANOVA with a post-hoc  
40 Bonferroni was used to identify differences between groups.

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

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

48 **Keywords**

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

50 **Introduction**

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

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

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

68 **Methods**

69 Ethics

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

72 Repeatability of the BIA-measurements

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

80 Subjects

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

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

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

#### 104 Study-design

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

#### 114 Statistics

115 To analyse the longitudinal evolution over the course of pregnancy, a longitudinal linear mixed model  
116 based analysis, which accounts for within-subject repetition (10), was performed in SAS (Version  
117 9.4/13.2) for all measurements of the UP-group. A sufficiently general model was fitted so as to avoid  
118 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  $\alpha=.05$ . 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.

126 **Results**

127 Repeatability of the BIA-measurements

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

133 Longitudinal evolution of fluid parameters

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

138 Demographics

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

149 Body fluids in uncomplicated and hypertensive pregnancies

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

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

156 **Comment**

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

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

173 *Longitudinal evolution of fluid parameters*

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

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

#### 187 Body fluids in uncomplicated and hypertensive pregnancies

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

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

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

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

224

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229 Oost-Limburg and Jessa Hospital.

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231

232 **Conflict of interests**

233 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)
<b>Weight before pregnancy [kg]</b>	70.72±16.76	73.94±16.71	1.00	68.53±18.04	1.00	69.00±12.11	1.00
<b>BMI before pregnancy</b>	25.3±6.1	26.5±5.0	1.00	24.7±5.7	1.00	23.7±9.0	1.00
<b>Weight at inclusion [kg]</b>	83.65±18.35	86.97±17.63	1.00	83.15±16.58	1.00	81.51±12.81	1.00
<b>BMI at inclusion</b>	29.9±6.7	31.3±5.5	1.00	32.0±13.4	1.00	30.9±4.6	1.00
<b>Gestational age at inclusion [weeks]</b>	<b>35.8±3.5</b>	<b>36.7±4.7</b>	1.00	<b>37.5±1.8</b>	.113	31.9±2.6	.004
<b>Gestational age at delivery [weeks]</b>	<b>39.0±2.4</b>	<b>38.6±2.0</b>	1.00	<b>38.0±1.5</b>	.154	32.3±2.5	<.001
<b>Foetal birth weight [g]</b>	<b>3320±668</b>	<b>3119±647</b>	.721	<b>2789±512</b>	<.001	1517±479	<.001
<b>Foetal birth weight centile</b>	<b>54.1±29.9</b>	<b>47.7±31.2</b>	1.00	29.6±23.8	<.001	19.3±14.6	.001
<b>Hematocrit [%]</b>	/	36.44±2.39	/	35.22±3.16	/	36.71±2.22	/
<b>GOT [ASAT] [U/L]</b>	/	20.16±18.34	/	24.41±27.21	/	20.55±9.54	/
<b>GPT [ALAT] [U/L]</b>	/	17.29±20.79	/	23.50±50.45	/	14.09±6.64	/
<b>Uric acid [mg/dL]</b>	/	5.47±1.60	/	5.84±1.30	/	6.32±1.54	/
<b>Proteinuria [mg/24 hours]</b>	/	<b>158±72</b>	/	<b>1343±1666</b>	/	2709±2984	/
<b>Antihypertensive medication [n (%)]</b>	0 (0%)	6 (17.6%)	<.001	8 (22.8%)	<.001	5 (45.5%)	<.001

235

236 Demographic characteristics of all groups presented as mean  $\pm$  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.

239 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
<b>TBW</b>	37.58±4.91	39.84±6.14	.330	<b>41.50±5.84</b>	<b>.003</b>	39.36±3.76	1.00
<b>ECW</b>	16.90±2.84	18.44±3.48	.140	<b>20.00±3.50</b>	<b>&lt;.001</b>	18.90±2.63	.310
<b>ICW</b>	20.55±2.50	21.40±2.84	.835	21.56±2.57	.336	20.46±1.34	1.00
<b>ECW/ICW</b>	0.815±0.07	<b>0.860±0.08</b>	<b>.041</b>	<b>0.922±0.09</b>	<b>&lt;.001</b>	<b>0.921±0.09</b>	<b>&lt;.001</b>

240

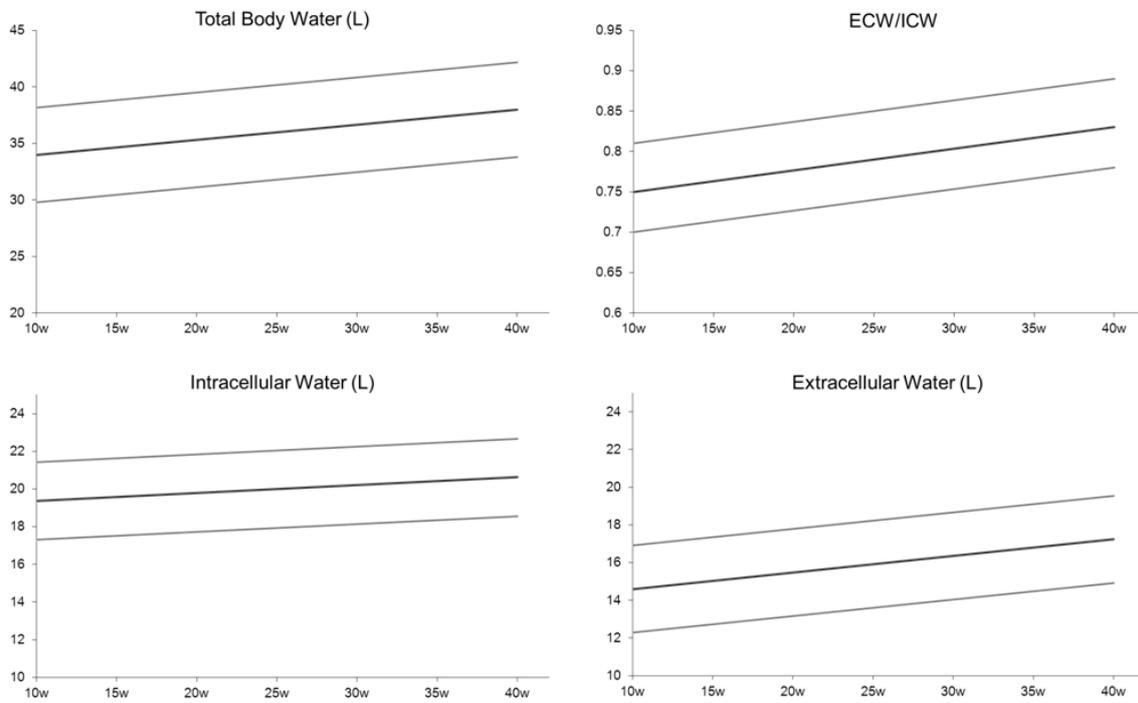
241 Data presented as mean ± standard deviation. P-values are reported relative to UP with significance differences marked in bold

242 TBW: Total Body Water, ECW: extracellular water, ICW: intracellular water, ECW/ICW: ratio between extracellular and intracellular water, UP:

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

244 **Figures**

245 Figure 1: Longitudinal evolution of fluid status during uncomplicated pregnancies



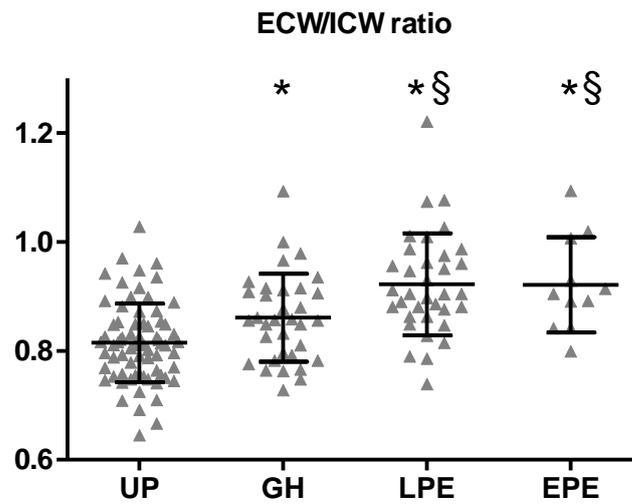
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247 Data presented as mean with standard deviation. All fluid parameters increase significantly ( $p < .001$ ).

248 ECW: extracellular water, ICW: intracellular water, ECW/ICW: ratio between extracellular and

249 intracellular water.

250 *Figure 2: The extracellular water/intracellular water ratio*



251

252 Data presented as scatter plots with mean and standard deviation. Groups significant different from  
253 UP are indicated with an asterisk (\*), and groups significant different from GH are indicated with §.

254 UP: uncomplicated pregnancies, GH: gestational hypertension; LPE: late-onset preeclampsia; EPE:  
255 early-onset preeclampsia.

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