

Low Volume Circulation in Normotensive Women Pregnant with
Neonates Small for Gestational Age

Peer-reviewed author version

VONCK, Sharona; Staelens, Anneleen Simone; LANSSENS, Dorien; TOMSIN, Kathleen; OBEN, Jolien; DREESEN, Pauline; BRUCKERS, Liesbeth & GYSELAERS, Wilfried (2019) Low Volume Circulation in Normotensive Women Pregnant with Neonates Small for Gestational Age. In: FETAL DIAGNOSIS AND THERAPY, 46 (4) , p. 238 -245.

DOI: 10.1159/000495507

Handle: <http://hdl.handle.net/1942/30363>

1 LOW VOLUME CIRCULATION IN NORMOTENSIVE WOMEN
2 PREGNANT WITH NEONATES SMALL FOR GESTATIONAL AGE

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14 Short title: Low volume circulation in small for gestational age pregnancies

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24
25 Keywords: small for gestational age; maternal hemodynamics; pregnancy; pathophysiology

26

27 **1. Abstract**

28 **Background**

29 Pregnancies complicated with small for gestational age (SGA) neonates are reported with
30 maternal circulatory maladaptations.

31 **Objectives**

32 We aimed to understand the pathophysiology of the maternal circulation in normotensive SGA
33 pregnancies and point the trimestral differences relative to those with appropriate-to-large
34 (non-SGA (NGA)) neonates.

35 **Methods**

36 An observational study was conducted in 3 trimestral cohorts of normotensive pregnancies,
37 categorized after birth according to neonatal birth weight percentile (BW%) as SGA ($BW\% \leq$
38 10 , $n = 158$) or NGA ($BW\% > 10$, $n=1038$). Standardized electrocardiogram-Doppler ultrasound,
39 impedance cardiography, and bio-impedance were used to assess the maternal heart, arteries,
40 veins and fluid.

41 **Results**

42 Diastolic blood pressure and mean arterial pressure were not significantly different, unless in
43 third trimester. In SGA, compared to NGA, total peripheral resistance (TPR) was higher and
44 total arterial compliance, cardiac output (CO) and total body water (TBW) were lower
45 throughout pregnancy. Venous return enhancing functions are activated. In NGA but not SGA,
46 a positive correlation was found between BW% and CO & TBW and a negative correlation
47 between BW% and TPR.

48 **Conclusions**

49 SGA pregnancies are characterized by lower maternal body fluid volume and CO, while normal
50 blood pressures are maintained via increased TPR already from first trimester onwards.
51 Pregnancy-induced hemodynamic changes are superimposed on these characteristics.

52

53 **2. Introduction**

54 Pregnancy needs a coordinated process at each level of the circulation: the heart, the arteries,
55 the microcirculation, the veins and the blood. A cascade of vasodilatation and lower blood
56 pressures followed by volume restoring mechanisms ensure an adequate uteroplacental blood
57 supply throughout pregnancy [1]. Many studies highlight an impaired cardiovascular adaptation
58 in different parts of the maternal circulation in pregnancies complicated by intra-uterine growth
59 restriction (IUGR) and/or birth of small for gestational age (SGA) neonates. Lower plasma
60 volumes [2], cardiac output [3] and/or smaller left atrial diameter were reported [3, 4]. This was
61 associated with higher total peripheral resistance [5], lower heart rate [4], lower stroke volume
62 [4], and higher blood pressures [4].

63
64 None of these studies however evaluated all aspects of the circulation simultaneously, or have
65 information in all trimesters. The pathophysiology can therefore only be explained partially. We
66 aim to investigate the maternal circulatory differences between normotensive pregnancies with
67 SGA neonates and appropriate/large (non-SGA (NGA)) neonates by applying a combined
68 assessment of the most important parts of the circulation (heart, central and peripheral arteries,
69 central veins and body fluid) during first, second and third trimester. We hypothesize that the
70 differences are type-specific.

71

72 **3. Materials and Methods**

73 **3.1 Patients**

74 Approval of the Ethical Committee was obtained before study onset (MEC ZOL, reference:
75 06/043, 08/049, 13/090U) and informed consent was obtained before inclusion. Women with
76 singleton pregnancies presenting at the obstetric ultrasound scanning clinic at Ziekenhuis
77 Oost-Limburg Genk between 1/1/2006-31/12/2016 were invited to participate in an
78 observational study on maternal cardiovascular function, as part of the ongoing Hasselt
79 University Study Project on Maternal Venous Hemodynamics. Three cohorts were considered:
80 women included in the first trimester (< 15 weeks), second trimester (15⁺⁰ to 27⁺⁶ weeks) and
81 third trimester (≥ 28 weeks). All women were invited for longitudinal measurements, of which
82 51% eventually did partly (2 trimesters) and 3,5% completely (3 trimesters), which gives this
83 study a cross-sectional semi-longitudinal character. After birth, the neonatal birth weight
84 percentile (BW%) was used to categorize these data as SGA (BW% ≤ 10) or NGA (BW% >
85 10). To determine if the SGA neonates were pathological or constitutionally small, the prenatal
86 umbilical artery PI (UA PI) was retrieved from the medical files: UAPI ≥ P95 was defined
87 pathologic and the other were considered normal. Normotension was defined as
88 sphygmomanometrically measured values < 140/90 mmHg in standing position. Multiplet
89 pregnancies (n=34) or women with chronic cardiovascular disease (n=42) were excluded from
90 this analysis, as well as women who developed gestational hypertension (n=136),
91 preeclampsia (n=246) or HELLP (n=32). Demographic details were maternal age,
92 pregestational BMI, gestational age at assessment and at delivery, parity, smoking,
93 medication, neonatal birth weight and percentile.

94

95 **3.2 Cardiovascular profile**

96 A maternal cardiovascular profile was assessed in every pregnant woman combining three
97 non-invasive techniques to obtain information about arteries, veins, heart, and body fluid
98 content. All patients had all assessments in 1 session and at least once during pregnancy. A

99 standardized protocol with known inter- and intra-observer variability was used as reported in
100 previous studies [6] .

101 *3.2.1 Impedance Cardiography (ICG)*

102 The Non-Invasive Continuous Cardiac Output Monitor (NICCOMO, Medis Medizinische
103 Messtechnik GmbH, Ilmenau, Germany) was used for automated blood pressure
104 measurements on the right arm and with an appropriate cuff width at standard time points. ICG
105 analysis was performed with four electrodes (two on the axillary line under the thorax and two
106 in the neck) eliminating skin resistance. The examination was performed after stabilization of
107 cardiovascular function in standing position. Parameters were classified into five groups: blood
108 pressures [systolic (SBP), diastolic (DBP), mean arterial pressure (MAP), pulse pressure (PP)],
109 flow parameters [heart rate (HR), stroke volume (SV), cardiac output (CO)], contractility
110 parameters [pre-ejection period (PEP), left ventricular ejection time (LVET), velocity index (VI),
111 acceleration index (ACI), heather index (HI)], thoracic fluid parameters [thoracic fluid content
112 (TFC)], vascular parameters [total arterial compliance (TAC), total peripheral resistance
113 (TPR)]. The latter was calculated using the formula $(MAP \times 80) / CO$ [7, 8].

114

115 *3.2.2 Electrocardiogram (ECG)-Doppler Ultrasound*

116 An ECG was combined with Doppler ultrasonography of the maternal renal interlobar veins,
117 hepatic veins and the arcuate uterine arteries using a 3,5 MHz transabdominal probe during
118 interrupted breathing in supine position (Aplio Mx, Toshiba Medical Systems nv, Sint-Stevens-
119 Woluwe, Belgium). Each parameter was measured three consecutive times and averaged as
120 part of a standardized protocol, reducing intra-variability [9]. Parameters of arteries and veins
121 were divided into 2 groups: pulse transit times and impedance indices.

122 The venous pulse transit time (VPTT) is the heart rate corrected time interval in ms between
123 the P-top from the ECG-wave and the A-wave from the Doppler pulse wave, divided by the
124 duration of the ECG R-R interval in ms. In the arteries (arterial pulse transit time, APTT), the
125 time interval starts at the Q-wave on the ECG and ends at the start of the Doppler end-diastolic
126 point D (QD in ms) [10].

127 At the venous side, the maximum and minimum flow velocity is measured from the renal and
128 hepatic Doppler signal. An impedance index is calculated using the formula [(Maximum
129 Velocity-Minimum Velocity)/Maximum velocity] [11, 12]. This renal interlobar vein index (RIVI)
130 and hepatic vein index (HVI) are considered the venous equivalents of the arterial Resistive
131 Index (RI) which is calculated by the formula (Peak systolic velocity – End diastolic
132 velocity)/Peak systolic velocity. In the uterine arcuate arteries, RI and Pulsatility Index (PI,
133 (Peak systolic velocity – minimal diastolic velocity)/Mean velocity) were measured as reported
134 [6, 13].

135

136 *3.2.3 Bio-impedance*

137 The body composition and fluid balance were measured by a multiple frequency bioelectrical
138 impedance analyzer (Maltron Bioscan 920-II, Maltron International LTD, Essex, UK) in supine
139 position with stretched arms and legs, without socks or shoes [14]. Two electrodes, receiving
140 the electrical signal, were placed on the dorsal surfaces of the wrist and ankle at the level of
141 the process of the radial and ulnar resp. fibular and tibial bones. Two other electrodes, sending
142 the electrical signal, were attached to the third metacarpal bone of the right hand and right foot.
143 The applied current was 0,6 mA with a frequency of 5, 50, 100, and 200 kHz during 5 seconds.
144 Total Body Water (TBW) estimated by bio-impedance is the total of intracellular water (ICW)
145 and extracellular water (ECW), which in turn includes interstitial, transcellular water, and
146 plasma volume.

147

148 **3.3 Statistics**

149 Normality was checked via Shapiro-Wilk. An independent t-test at 5% significance level was
150 used to compare SGA and NGA for continuous demographic data. Chi-square test was used
151 for categorical demographic variables. These data were presented as mean \pm SD or n (%).

152 Linear Mixed Models for repeated measurements were used to examine differences between
153 SGA and NGA and between trimesters. A random patient effect was used to correct for the

154 correlation between trimestral measurements of a pregnancy. Fixed effects of trimester and
155 group (SGA or NGA), as well as their interaction term were specified. The fixed effects
156 structure was simplified by using a significance level of 5%. Analyses were done in SAS (SAS
157 9.4, Institute Inc., Cary, NC, USA). The impact of demographical influences (BMI, smoking,
158 nulliparity, and age) on the cardiovascular parameters was assessed by adding these patient
159 characteristics in the linear mixed model. Corrections for multiple testing were not
160 implemented.

161 Pearson Correlation Coefficient was calculated to assess the relation between BW% and CO,
162 TPR & TBW.

163 **4. Results**

164 A total of 1196 normotensive pregnant women were included, of which 158 delivered SGA and
165 1038 NGA neonates. For 541 pregnancies, a cardiovascular assessment was done only in
166 one trimester, for 611 pregnancies cardiovascular data were collected in two trimesters and
167 finally for 44 pregnancies cardiovascular data for all three trimesters were present. Numbers
168 of pregnancies with a cardiovascular assessment in each trimester for SGA and NGA are
169 presented in Figure 1.

170

171 Patient and outcome characteristics are enlisted in Table 1. For 69/158 (44%) SGA infants a
172 PI measurement was found, of which 60 (87%) were <95th percentile. The growth of SGA
173 neonates without umbilical artery Doppler measurements (56%) was considered normal at
174 routine third trimester ultrasound scan, and therefore no Doppler assessments were
175 performed. As such, the majority of SGA neonates (94%) in our population were considered
176 not pathologically but simply constitutionally small, however missed diagnosis of late IUGR
177 cannot be excluded.

178

179 Detailed hemodynamic features are listed in Table 2. Figure 2A presents the difference of
180 TBW, CO, DBP and TPR in first, second and third trimester. Except for TPR and CO, all

181 parameters showed a similar change throughout the pregnancy in both groups. In each
182 trimester, CO, HR, and SV were lower and TPR higher in the SGA group compared to NGA
183 (Table 2). DBP and MAP were not different in the first and second trimester, but were higher
184 in the SGA group in third trimester (Figure 2A, Table 2). As compared to NGA, SGA showed
185 for HR, CO, SV, TBW, TAC, right APTT, and all VPTT's lower values in first trimester, whereas
186 TPR, HVI, left PI & RI were higher. CO increased from first to second trimester in both NGA
187 and SGA, but in the third trimester a decreasing trend was observed in SGA, whereas there
188 was an increasing trend in NGA (Figure 2A, Table 2). TPR decreased from first to second
189 trimester in both NGA and SGA and increased again in third trimester (Figure 2A, Table 2).
190 This TPR rise was more pronounced for SGA than NGA (Figure 2A). TBW increased from first
191 to third trimester, but all values of the SGA group were lower (Figure 2A). Venous and arterial
192 pulse transit times rose with gestational age, whereas impedance parameters decreased
193 (Figure 2B).

194

195 As is shown in Table 3, there were weak, but significant correlations between BW% and CO,
196 BW% and TPR, BW% and TBW, BW% and ECW in the NGA group, present at each trimester.
197 In the SGA group, none of those correlations were significant.

198

199 **5. Discussion/Conclusion**

200 Our analysis gives a global hemodynamic view on the circulation of normotensive women
201 pregnant with SGA neonates, which is clearly different from pregnancies with NGA neonates.
202 In SGA (1) a lower maternal body fluid volume and CO is already present from the first trimester
203 onward, meanwhile blood pressure is maintained normal via a higher TPR; (2) cardiac output
204 fails to increase from second to third trimester; (3) venous return enhancing function is more
205 active and (4) the correlation between BW% and CO, TPR or TBW in NGA pregnancies is
206 lacking in SGA.

207

208 Our study is one of the first to assess the complete cardiovascular system as a functional
209 circuit: volumes, heart, arterial and venous hemodynamics are evaluated in one simple
210 session. A standardized protocol using non-invasive techniques with known inter- and intra-
211 observer variability is applied [9]. Bio-impedance may be criticized as being less valid than
212 maternal echocardiography or dye dilution plasma volume measurements, however our results
213 are in line with these so-called gold standard methods [15]. It should be appreciated that the
214 bio-impedance methodology is very easy to perform and shows very low inter- and intra-
215 observer variabilities, allowing a general application by any (para)medical health care worker
216 with a minimum of training or expertise. However, our findings need to be confirmed by other,
217 preferably gold-standard techniques. We acknowledge that the number of pregnancies with
218 longitudinal measurements in each trimester is low and no correction for multiple testing was
219 performed, due to which some of the significant results can still relate to chance. Further, we
220 would like to address a possible misclassification of a number of NGA fetuses, also suffering
221 from growth restriction but with the birth weight above the 10th centile, similar to maternal
222 smoking or residing in an air polluted environment.

223

224 Blood pressures in first trimester are within the normal reference range in SGA and NGA, but
225 its components, CO & TPR, differ significantly between SGA and NGA [3-5]. As such, this
226 illustrates a false clinical perception of normal maternal hemodynamics via measurement of
227 normal blood pressures in the SGA group. A positive correlation between TBW and plasma
228 volume has been reported [16]. Plasma volume, a component of TBW, has repeatedly been
229 reported to be lower in SGA pregnancies [2, 5], and this condition is associated with lower
230 preload, SV and CO [5, 17-19]. Despite the effect that we cannot exclude a low amniotic fluid
231 volume interfering with the measured value of TBW, our results of low BW and CO in SGA are
232 in line with these reports. On top of this, our data link maternal low volume status to abnormal
233 circulatory function throughout pregnancy, with failure of appropriate increase of cardiac output
234 despite venous return enhancing activity. When approaching term, blood pressures rise
235 gradually, driven by neurohormonal control mechanisms coordinating the balance between

236 vascular tone and volume [20]. In SGA however, there is a lack of sufficient body fluid volume,
237 which reflects a failure to further increase the CO (Figure 2A). It is still unclear whether this is
238 due to a pregestational venous underfilling [21, 22], or to an impaired gestational expansion
239 process [5, 23]. Additionally, in our study, low VPTT's are present in SGA, which can be
240 considered a reflection of higher venous activity trying to increase the venous return and
241 preload to accommodate CO at the expense of the venous reserve capacity [2]. Reduced
242 APTT and TAC, together with a higher PI, RI and TPR in SGA [5, 24], reflect an overall
243 increased arterial resistivity to maintain a normal blood pressure by rising the afterload. This
244 results in higher blood pressures in SGA in third trimester, however still within the acceptable
245 clinical reference ranges. Both in normal and hypertensive pregnancies, higher blood
246 pressures have a negative impact on birth weights [25].

247

248 For uncomplicated pregnancies, a correlation between maternal cardiac output and neonatal
249 birthweight has been reported, both during pregnancy [26, 27] as in the transition period from
250 preconception to mid-pregnancy [28]. An additional novelty in this study is the lack of
251 correlation between SGA BW% and CO, which is in contrast with normotensive NGA
252 pregnancies [26, 27] (Table 3) and with those we formerly reported for preeclampsia [29],
253 resulting in the birth of a healthy baby with birth weight low for gestational age. Similarly, the
254 positive correlation between BW% and TBW was only found in NGA but not in SGA
255 pregnancies [30, 31]. Higher values of TPR were reported for advanced SGA pregnancies [27,
256 32], together with an inverse correlation between TPR and BW% [4, 32]. We found that - to a
257 lesser extend – this was also true in first and second trimester for NGA, but not for SGA.

258

259 Our observations have important implications to both clinical practice and research settings.
260 Clinicians should be aware that a normal blood pressure does not necessarily reflect normal
261 maternal haemodynamic function, as this may be present with abnormally high peripheral
262 resistance in combination with low cardiac output or vice versa. In order to better appreciate
263 the true relevance of maternal blood pressure, it seems appropriate to measure its physiologic

264 components being cardiac output and peripheral resistance. Our data offer a simple way to
265 understand the pathophysiology of SGA without the need to explain the aetiology. It addresses
266 clearly the fact that maternal hemodynamics should be visualized as a closed circuit, where
267 heart, arteries, veins and microcirculation are indistinguishably linked to each other. These
268 results open the discussion whether low maternal body fluid content is a maternal precondition
269 or develops after abnormal placentation. Our study supports the exploration of therapeutic
270 intravascular volume expansion as prevention for SGA births when detecting low maternal
271 body fluid content.

272 **8. Statements**

273 **8.1 Acknowledgements**

274 The authors like to acknowledge Prof. dr. Robert Pattinson, University of Pretoria,
275 South-Africa, Dr. Kristof Thevissen, Ziekenhuis Oost-Limburg, Belgium and Prof. dr.
276 Christoph Lees, Imperial College London, UK for their valuable and constructive
277 comments. All authors are part of the Limburg Clinical Research Project (LCRP) at
278 Hasselt University, Belgium.

279 **8.2 Statement of Ethics**

280 Subjects have given their written informed consent and the study protocol was
281 approved by the local ethical committee.

282 **8.3 Disclosure Statement**

283 The authors report no conflict of interest.

284 **8.4 Funding Sources**

285 The first author of this work is funded by a Ph.D. grant of the Agency for Innovation by
286 Science and Technology (IWT) in Brussels, Belgium.

287 **8.5 Author Contributions**

288 WG + SV: study design, patient inclusion, data management, writing the article

289 LB: statistics

290 ASS, DL, KT, JO, PD: patient inclusion

291

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397

398 **10. Figure Legends**

399 Figure 1: Flowchart from pregnancies included in the observational study as part of the Hasselt
400 University Study Project on Maternal Venous Hemodynamics. 1196 normotensive pregnancies
401 were categorized after birth into Appropriate for Gestational Age (-SGA, represent NGA) and
402 Small for Gestational Age (SGA), based on birth weight percentile. Assessments per patient
403 were done in the first, second or third trimester (1T, 2T, 3T resp.) alone or in multiple trimesters.
404 *GH: Gestational Hypertension, LPE: Late Preeclampsia, EPE: Early Preeclampsia; EH:*
405 *Essential Hypertension*

406 Figure 2: Average hemodynamic evolution of A: Total Body Water, Cardiac Output, Diastolic
407 Blood Pressure and Total Peripheral Resistance; B: left uterine Pulsatility Index, right Uterine
408 Artery Pulse Transit Time, Total Arterial Compliance and hepatic Vein Pulse Transit Time
409 between normotensive women, giving birth to neonates Appropriate for Gestational Age (NGA,
410 white) and Small for Gestational Age (SGA, black). Data are presented as least-square means
411 \pm SD. $p < 0,05$ was considered significant. *Significant difference between trimesters in NGA or
412 SGA. #Significant difference from uncomplicated pregnancy in the same trimester.