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

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

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1. Abstract

Background

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

Objectives

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

Methods

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

Results

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

Conclusions

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

2. Introduction

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

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

3. Materials and Methods

3.1 Patients

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

3.2 Cardiovascular profile

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

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

3.2.1 Impedance Cardiography (ICG)

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

3.2.2 Electrocardiogram (ECG)-Doppler Ultrasound

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

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

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

3.2.3 Bio-impedance

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

3.3 Statistics

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

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

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

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

4. Results

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

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

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

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

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

5. Discussion/Conclusion

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

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

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

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

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

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

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

8. Statements

8.1 Acknowledgements

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8.2 Statement of Ethics

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

8.3 Disclosure Statement

The authors report no conflict of interest.

8.4 Funding Sources

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8.5 Author Contributions

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

LB: statistics

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

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10. Figure Legends

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

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