Assessment of venous hemodynamics and volume homeostasis during pregnancy: recommendations of the International Working Group on Maternal Hemodynamics

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Title

Assessment of venous hemodynamics and volume homeostasis during pregnancy

Short title

Veins and Volume

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Short abstract

Venous hemodynamics and volume homeostasis are important aspects of cardiovascular physiology, however today their relevance is still very much underappreciated. Their most important role is maintenance and control of venous return and as such cardiac output. A high flow/low resistance circulation, remaining constant under physiological circumstances, is mandatory for an uncomplicated course of pregnancy. In this paper, characteristics of normal and abnormal venous and volume regulating functions are discussed with respect to normal and pathologic outcomes of pregnancy, and current (non-invasive) methods to assess these functions are summarized.

Introduction

Cardiac and arterial hemodynamics are mainly driven by positive pressure gradients between the heart and peripheral tissues, created by high energetic forces. Venous hemodynamics on the contrary mainly functions with low powered volume shifts, achieved via mobilization or storage of venous blood. Selective redirection of non-actively circulating volumes from capacitance vessels into the circulation is possible by changes in venous vascular tone, served by endothelial function and autonomic nervous stimulation. Volume expansion is known to be an important aspect of normal gestational physiology. Abnormalities in volume homeostasis may lead to inadequate performance of the gestational high flow/low resistance circulation, and this predisposes to abnormal outcomes for both mother and child. In this paper, current (non-invasive) methods to assess venous hemodynamics and volume regulation in pregnant women are summarized, and some recommendations are formulated for future research before, during and after pregnancy.

1. PHYSIOLOGY OF THE VENOUS COMPARTMENT AND PLASMA VOLUME

Normal venous hemodynamics

The histological structure of the venous vascular wall serves the three main physiologic functions of the venous compartment: a) control of cardiac preload, and as such cardiac output, b) storage and mobilization of blood, and c) regulation of microcirculatory flow.

The inner layer of the venous wall contains heterogeneous endothelial cells with different functions depending on their location. These endothelial cells are part of the dynamic organ lining of the entire vascular system (1). Elastin and collagen fibers of the adventitia are passive tension elements necessary for vessel wall distensibility. Both passive tension and active vascular smooth muscle cell contraction interact strongly to determine vessel wall compliance (2). Veins have 30 times greater compliance than arteries, i.e. a great change in volume causes only a small change in pressure and small changes in venous tone mobilizes large volumes of blood with major effects on cardiac pre-load. Consequently, the veins are able to significantly influence the distribution of large volumes of blood throughout the human body, and therefore determine most of the vascular capacitance (3). Thus as veins, heart, and arteries together constitute a closed circuit, venous return is a major player in determining cardiac output. Specifically, a reflex-induced venoconstriction can mobilize stored blood to preserve venous return to the heart, and as such cardiac output, in specific circumstances like hypovolemia (4). This is an important characteristic of venous hemodynamics, which is served by the functional integrity of the venous endothelium in cooperation with a richly innervated sympathetic network (2, 5). The sympathetic nervous system is the most important vasopressor system in the control of venous capacitance (2, 6). In the presence of resting sympathetic tone, 60-70% of total blood volume is localized in the venous compartment and serves predominantly as blood volume reservoir, which is mainly located in the splanchnic circulation and the liver (6, 7).

Endothelial cells respond to hormones, neurotransmitters, and vasoactive factors, thereby indirectly influencing the underlying vascular smooth muscle cells through release of nitric oxide, prostacyclin,

thromboxane, endothelin, and by means of hyperpolarization (1, 5). On top of this, the endothelium can be activated by changes in flow-dependent shear stress, which results from the viscosity and flowing movement of the blood, and from the vessel wall tension and diameter (2, 7).

Because of the anatomical position between the arterial and venous compartments, capillary blood flow is influenced by both arterioles and venules in antegrade or retrograde directions respectively (8). Arteriolar constriction and dilatation serves the distribution of cardiac output towards and inside the different organ systems (2, 9). Only a small increase of intravenular pressure already will cause a deceleration, arrest or even reversal of capillary blood flow, which can lead to increased transcapillary exsudation of water, electrolytes and proteins into the surrounding tissues. Next to this, increased intravenular pressure induces a reflex arteriolar constriction, leading to arterial hypertension but also reduction of capillary influx in order to prevent capillary damage at the cost of flow (8, 10). Next to this, the microcirculation is also protected by the opening of protective arteriovenous shunts, bypassing the vulnerable microcirculation and preventing massive edema formation. The opposite events occur when the intravenular pressure decreases (8).

The driving force behind forward venous blood flow is totally different from that in arteries. Arterial flow results from positive “pushing” forces created by the cardiac systole, whereas venous flow is mainly a consequence of negative “suction” forces caused by negative intra-thoracic pressure during inspiration and concomitant pressure changes in the right atrium throughout the cardiac cycle (4). The characteristics of the venous pulse wave are related to the cyclic changes of right atrial pressure (Figure 1). The A-wave represents transient venous deceleration or even reversal of forward flow, caused by retrograde pressure from the contraction of the right atrium by lack of a valve mechanism between the right atrium and the venae cava. The X-descent, is a temporary acceleration of forward flow, which relates to the fast filling of the right atrium during atrial relaxation, which is followed by the V-deceleration of forward venous flow at filling of the right atrium with closed tricuspid valve. Ventricular diastole with open tricuspid valve allows rapid emptying of the right

atrium into the right ventricle and creates a suction force relative to the atrioventricular and central venous pressure gradient, which in turn induces fast forward venous flow velocity, labelled as the Y-descent. When both ventricle and atrium are filled with blood, venous forward flow decelerates again instants before a new atrial contraction (11). The shape of venous waveforms is influenced by many physiologic variables. Triphasic waves are mostly found close to the heart (hepatic veins, jugular vein), whereas at a longer distance more flattened waves are present (femoral vein). Flow velocities decrease during inspiration and accelerate during expiration. Increase of intra-abdominal pressure during Valsalva manoeuver causes a shift from triphasic to flat hepatic vein Doppler patterns, whereas intravenous fluid load accentuates the triphasic pattern. Other interfering variables are orthostasis, gravity, muscle pump activity, external compression or intra-abdominal processes inflicting venous flow such as a tumor, gravid uterus or increased intra-peritoneal pressure during laparoscopy (4, 12, 13). These inferences highlight the need for standardization of the venous Doppler assessment via patient positioning in relaxed conditions, and controlled breathing with instructed breath hold.

Normal regulation of plasma volume

In healthy individuals, plasma volume is kept relatively constant by a complex interaction between neuro-humoral systems involved in sodium and water homeostasis. The three major players in regulation of the plasma volume are the volume, the osmolality and the pressure receptors. The key receptors monitoring volume status are stretch receptors in the cardiopulmonary circulation, the atria, the carotid sinus, the aortic arch, and the juxtaglomerular apparatus of the kidney.

The extra-renal stretch receptors rule the activity of the sympathetic nervous system and the production of atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH). In states of volume depletion, sympathetic neural tone and the secretion of catecholamines by the adrenal medulla are enhanced. Opposite, in response to volume expansion, increased cardiac preload leads to atrial stretch causing ANP release by the cardiac atria to lower excessive intra-vascular volume (14). As a

consequence, ANP subsequently increases glomerular filtration rate, decreases sodium retention in the proximal tubule and collecting ducts of the kidney and increases capillary leakage. The renal receptors affect volume balance by influencing the renin-angiotensin-aldosterone system (RAAS) and endothelial nitric oxide (NO) production. Renin secretion increases when circulating volume and renal perfusion pressure decreases (15). Renin stimulates the conversion of angiotensinogen into angiotensin. Angiotensin has two major actions by increasing the secretion of aldosterone from the adrenal cortex: arterial vasoconstriction and renal sodium and water retention (16-18).

Secondly, ADH or vasopressin is released by the pituitary gland predominantly in response to hyperosmolality, sensed by hypothalamic receptors, and to a lesser extent to volume depletion, sensed by receptors in the carotids (19). ADH augments water permeability in the collecting tubules of the kidney, hence promoting water reabsorption.

In addition to the stretch and osmolality receptors, pressure receptors (baroreceptors) mainly located in the carotid arteries and aortic arch, respond to variations in blood pressure by acting on the interplay between the sympathetic and parasympathetic nervous system altering cardiac inotropy and chronotropy and vascular constriction (15). Effects of the baroreceptors may indirectly influence plasma volume status by acting on the volume capacity of the vascular system, primarily the venous system (20).

2. NORMAL GESTATIONAL CHANGES OF VENOUS HEMODYNAMICS AND PLASMA VOLUME

Venous hemodynamic changes in normal pregnancy

During normal pregnancy, important changes of central venous blood flow occur. At the level of the kidneys, venous flow velocities increase during the first trimester to reach a plateau level in the second trimester, followed by a decrease in the third trimester (21). These effects are more prominent in the right than in the left kidney most likely as a consequence of inter-renal anatomical differences (21). The change of minimum flow velocity is higher than that of maximum flow velocity, Changes in flow velocity result in a gradual flattening of the venous pulse wave. This effect is very prominent at the level of hepatic veins (HV), where the first trimester triphasic venous pulse wave shifts to a completely flat pattern during the late second and third trimester (22). These changes co-exist with important physiological gestational adaptations of the maternal body, amongst which are an increase of venous return and intravascular volume by altered renal function (vascular perfusion and drainage, glomerular and tubular function, hormonal production and response) (23), a coordinated balanced change of baroreflex sensitivity of heart and vasculature (24), and raised external venous compression by increase of intraabdominal pressure (25). The latter also contributes to the development of varicose veins and physiological malleolar edema during the course of pregnancy (26).

Another important change of venous hemodynamics during normal pregnancy is a reduction of venous vascular tone. This is reflected in an increase of venous pulse transit time (VPTT), defined as the time interval between the electrocardiographic (ECG) P-wave, which initiates atrial contraction, and the venous Doppler A-wave, which results from atrial contraction (Fig 1) (27). The gestational evolution of venous pulse transit time is shown in Figure 2. There is a linear correlation between the stiffness of the vessel wall and the speed at which a pulse wave propagates through the lumen, measured as pulse wave velocity or pulse transit time (28). As explained above, venous vascular tone results from combined effects by the endothelium and the autonomic nervous activity. Normal

pregnancy is characterized by reduced parasympathetic responsiveness, resulting in a predominant sympathetic stimulatory effect on vascular tone of capacitance vessels (29). The combination of reduced pulse wave velocity with sympathetic dominance during normal pregnancy indicates that (a) the venodilatation is mainly endothelium derived, (b) the augmented capacitance function of the venous compartment is associated with increased mobilization capacities of the venous system to shift stored blood into the circulation. These functionalities are very relevant to the important shift of the maternal circulation from a low flow/high resistance to a high flow/low resistance state (30).

Changes of plasma volume during normal pregnancy

The circulatory requirements rapidly increase in pregnancy from as early as 5 weeks onwards. Cardiac output rises, most likely as a combined result of the opening of protective micro-circulatory arterio-venous shunts and a tremendous drop in arterial tone, leading to a substantial drop in total peripheral vascular resistance (31). Animal and laboratory experiments suggest that these changes are endocrine driven, leading to vasodilation by up-regulating endothelium dependent NO pathway, decreasing responsiveness to vasoconstrictor stimuli, reducing myogenic reactivity and increasing arterial compliance (32-53). As observed in early human pregnancy, due to decreased peripheral vascular resistance, arterial blood pressure drops, which, in turn, activates numerous compensatory mechanisms to balance the sudden reduction in cardiac afterload. The heart rate and stroke volume rises and the sympathetic tone, the volume retaining RAAS and the venous tone increase, to compensate for the reduced pressure load, until plasma volume has restored. At this stage, venous filling, instead of tone, warrants preload (54, 55). Mostly, the initial drop in peripheral vascular resistance can easily be balanced via mobilization of unstressed venous circulatory volume, large enough to compensate for the sudden loss of arterial filling. It is generally thought that, in case of shallow venous reserves, problems in initial circulatory adaptation may precede clinical overt maternal hypertensive disease and/or fetal growth restriction.

Plasma volume rapidly increases during human pregnancy. In a recent systematic review and meta-analysis, it was detailed that in uneventful gestation, as early as in the first trimester, plasma volume increases 180 ml (95% CI 120-240ml) as compared to the non-pregnant condition. Plasma volume continues to rise until term up to 1130ml (95%CI 1070-1190ml), but has it steepest increase throughout the second trimester (56) (Figure 3).

Physiological relevance of gestational adaptations of the venous system and plasma volume

From pregestation to late third trimester, there is a 4-fold increase of uterine perfusion and uterus-directed fraction of cardiac output (57). This increased uterine demand should go without disturbing the functionality of other organ systems. This is only possible when the feeding and drainage needs of the uterus and its contents are anticipated by major hemodynamic changes. In this, both the venous compartment and blood volume are involved. The placental maternal-fetal exchange is optimized by shifting the normal low flow /high resistance of the uterine circulation towards a high flow/ low resistance state by the mechanisms explained above. Together with this, there is an increased transcapillary molecular transfer from intra- to extra-luminal side, which presents clinically as subcutaneous and interstitial edema, increased glomerular filtration and micro-albuminuria, and increased thoracic interstitial fluid (58). These circulatory changes all facilitate maternal supply of oxygen and nutrients to the growing fetus, while remaining enough reserve capacity for the mother. The relevance of the venous hemodynamic function in this process is illustrated by the correlation of hepatic vein blood flow characteristics and fetal birth weight (59).

3. MALADAPTATIONS OF VENOUS HEMODYNAMICS AND PLASMA VOLUME IN PATHOLOGIC PREGNANCY

Characteristics of venous waveforms depend on type of hypertension

In hepatic veins of preeclamptic patients, the normal transition from a triphasic to a flat pattern does not always occur. During early-onset preeclampsia, triphasic HV patterns are observed instead of a flat pattern. This seemingly looks like the woman is either not pregnant at all, or remains in the first part of pregnancy (27). It should be emphasized that the HV waveforms are not always identical at different locations of the hepatic venous tree: some parts of the liver may contain triphasic patterns whereas simultaneously, other areas show flat types. This has been observed in normal pregnancy, preeclampsia and also during HELLP-crisis (unpublished data).

Renal Interlobar Vein Impedance Index (RIVI), defined as [(max flow – min flow)/max flow], is higher in early-onset preeclampsia than in normal pregnancy (21, 60). Increased RIVI values are mainly due to a sharp deceleration of forward venous flow, the so-called venous pre-acceleration nadir (VPAN), which is time-related to the P-wave of the maternal ECG. This represents backflow of venous blood during atrial contraction up to the level of the kidneys, which might relate to cardiac diastolic dysfunction or reduced venous distensibility (27). This indicates that during preeclampsia, the venous backflow of blood during atrial contraction travels faster and further upstream than in uncomplicated pregnancy (61) . In late-onset preeclampsia however, RIVI values are often within the normal range (60). The undulating pattern of weekly RIVI measurements is more pronounced in preeclampsia than in uncomplicated third trimester pregnancies, and contrary to the non-pregnant conditions, shows a simultaneous pattern in both kidneys (62). Abnormal RIVI values are observed weeks before clinical onset of preeclampsia, and again, this is mainly true for early-onset preeclampsia (63).

VPTT is shorter in preeclampsia than in normal pregnancy, and this is more pronounced in early- than in late-onset preeclampsia (61, 64) PE-related shortening of VPTT occurs simultaneous at te arterial

and venous sites, reflecting stiffening of the vascular wall, probably due to increased vascular tone (64).

Contrary to observations in preeclampsia, in non-proteinuric gestational hypertension, venous Doppler wave measurements are not different from uncomplicated pregnancies (61, 65). This suggests that venous hemodynamic dysfunction seems to be a pathophysiological feature of preeclampsia but not gestational hypertension. In this perspective, the reported correlation between RIVI and degree of proteinuria in late-onset preeclampsia is very interesting (65). These observations warrant further documentation by clinical and laboratory experiments.

Plasma volume before and during pathological pregnancy

Until term, plasma volume increases irrespective of later maternal hypertensive complications or fetal growth restriction (66-68). In the latter two subgroups, plasma volume may be consistently lower throughout the course of gestation, long before clinical problems occur. Plasma volume could also be shallow already before pregnancy, without changing the pattern of adaptation (54, 56, 66, 69, 70). On the other hand, low plasma volume at term may also originate from loss in circulatory volume resulting in edema formation, often seen in preeclampsia.

Shallow plasma volume most likely does not relate to arterial underfilling but merely reflects reduced venous reserves. During the early follicular phase, directly after the menstrual period, when women can be considered at baseline hemodynamic influence by sex hormones, women with low plasma volume do not display neuro-humoral alterations such as elevated renin, angiotension and aldosterone levels or higher levels in epinephrine or norepinephrine (54, 55, 69-71). Next to this, venous compliance is reduced in women with low plasma volume, as well as dynamic capacity to increase venous tone during orthostatic challenges (72-74). These women also show a reduced static capacitance to hold extra-added venous fluid without increasing venous pressure and cardiac preload (54, 55, 66-73, 75). These observations support the view of low plasma volume reflecting reduced venous reserve capacity (72, 73, 75).

But why is plasma volume low in these formerly preeclamptic women? One hypothesis is that the venous compartment is constitutionally smaller, affecting both capacity and capacitance. Recent observations detail the linear effect of own birth weight on later grown-up plasma volume in which multivariable analysis show that birth weight accounts for 14% in total adult plasma volume (74). Human studies on venous functions related to the fetal origins of adult system biology are lacking. On the other hand, venous function can be reduced by functional changes through (1) primarily increased sympathetic tone or increased autonomic sensitivity influencing capacity and (2) increased smooth muscle contraction with secondary increased muscle and collagen mass, primarily affecting capacitance. As stated, low plasma volume not only correlates with reduced venous compliance, it also relates to increased sympathetic tone and reduced venous capacitance. Moreover, the venous responsiveness to head up tilt is decreased in women with low plasma volume (72, 73, 76, 77). These observations suggest at least an interrelated role for sympathetic dominance and low plasma volume. Whether or not the venous wall mass has gained increased stiffness through increased muscular or connective tissue remains to be elucidated. Finally, increased tone could also originate from venous endothelial dysfunction. Recent observations indicate reduced arterial endothelial function in formerly preeclamptic women in the first year after birth, improving towards the level found in sedentary healthy parous women after increasing physical exercise. It is unclear whether this is also true for the venous endothelium (78, 79).

Women with a history of preeclampsia are at increased risk for recurrent gestational hypertensive disease. More than half of these women have low plasma volume at follow-up in the first year after birth (70, 80). Functionally, pre-pregnancy low plasma volume predisposes to subsequent early pregnancy circulatory maladaptation (54). In these cases, in response to the volume-retaining stimulus of early pregnancy, women showed increased plasma volume without increasing venous compliance. Meanwhile, ANP- rises, which in turn correlates with blunted plasma volume expansion. These data suggest venous overfill in early pregnancy. Apparently, the increased plasma volume cannot be accommodated in the venous compartment, leading to increased cardiac preload and the

observed rise in ANP. Clinically, the lower the pre-pregnancy plasma volume, the higher the risk on recurrent gestational hypertensive disease, from about 1 in 20 formerly preeclamptic women in the highest plasma volume quartile (corresponding normal plasma volume as observed in healthy parous controls) to 1 in 3 formerly preeclamptic women in the lowest plasma volume quartile (81). Moreover, the size of the plasma volume relates to preterm birth and birth weight centile in these women. Therefore, knowing the plasma volume may be helpful in assessing personalized recurrence risks for women in the preconceptional phase. Life style changes, such as exercise, have proven plasma volume modulatory properties (76-79). Physical training before and during pregnancy may reduce the risk on preeclampsia (82, 83). Since life style changes lead to improved pre-pregnancy hemodynamic and autonomic function, it is worthwhile exploring whether in formerly preeclamptic women, the resulting change in plasma volume relates to a corresponding change in recurrence risk. If so, knowing the person's plasma volume could also affect the type of pre-pregnancy life style recommendations given to these individuals.

In preeclampsia, absolute plasma volume may be reduced, but relative plasma volume may be sufficient or even increased. In case of reduced venous dimensions, constitual or functional, sympathetic overactivity and venous constriction concur to meet the arterial demands. Consequently, plasma volume expansion without concomitant sympaticolytic or vasodilatory agents is likely to lead to venous overfill and with it ANP- induced capillary leakage and (pulmonary) edema formation, especially when volume loading is performed in relative short time. Without accounting for and monitoring the receptivity of the venous system to be able to accommodate extra fluid, on top of the often already present endothelial dysfunction related capillary leakage, this sequence of events may underlie the negative results of intervention trials with plasma volume expansion (84, 85).

METHODS TO ASSESS VENOUS HEMODYNAMICS AND PLASMA VOLUME

Venous hemodynamics

The assessment of hemodynamic characteristics of the venous compartment is much more difficult than in the arterial system, and have been reviewed extensively by Pang (29, 86). Methods such as the measurement of Mean Circulatory Filling Pressure or Constant Cardiac Output Reservoir are only applicable under experimental conditions or with anesthesia and extensive surgery (29). Blood pool scintigraphy requires the use of radiolabeled albumin and therefore is not suitable for application during pregnancy (29). Venous occlusion plethysmography and the Linear Variable Differential Transformer Technique evaluate local peripheral venous function, of which the physiologic functions and reflex control mechanisms are totally different from the central and intra-abdominal veins (3, 87), and therefore these measurements do not always reflect venous circulatory control events (29). The methods for venous hemodynamics assessment, reviewed in this paper, are limited to those addressing the balance between circulating and stored blood volumes in pregnant women. For this, only abdominal ultrasound and Doppler sonography have been proven useful today.

Limited data are available on ultrasound assessment of inferior vena cava dimensions and collapsibility during in- and expiration in normal and complicated pregnancies. The diameter of vena cava changes significantly after intravenous volume load (88) or changed maternal position (89) in uncomplicated, term pregnancy. Compared to normal pregnancy, vena cava collapsibility index, defined as 100% x (Ø expiration – Ø inspiration)/Ø expiration, is reduced in both late onset preeclampsia (90) as in preeclampsia with fetal growth restriction (91).

A standardised Duplex ultrasound examination has been reported, which enables the acquisition of reproducible data for venous flow velocities and venous impedance indices. Here both kidneys and liver are scanned in the transverse plane (Figure 4) to allow for the correct identification of renal interlobar veins, as well as the three branches of the hepatic veins, with no more than 30 degrees of angle correction. As for arterial Doppler flow assessment, methodological standardization is needed for venous Doppler sonography, especially when the above-mentioned confounding factors are to be excluded. The impact of breathing movements is minimalized by the recording of at least 2–3 similar

Doppler flow patterns during interrupted breathing (22). For this methodology, intra-class correlation coefficients improve markedly by a) the use of repeated measures, b) the addition of the maternal ECG and c) training (92).

For each of the veins, the time-interval between the ECG P-wave and the corresponding venous Doppler A wave is measured (64). As the heart rate increases with advancing gestation, these time-intervals are expressed relative to the ECG-wave duration measured between two consecutive R peaks. It was calculated that a mean value of three consecutive measurements allows obtaining reproducible Doppler flow indices at the level of renal interlobar and hepatic veins with intra-class correlation coefficients ≥ 0.8.

It should be emphasized that venous Doppler flow measurements can be troubled by inter-individual anatomical variations, which are much more pronounced in the venous than in the arterial compartment (93), and by specific diseases or organ pathologies interfering with the shape of venous Doppler waves and value of venous flow measurements, such as chronic liver or kidney disease, hydronephrosis, auto-immune vasculitis and obesity (94).

Plasma volume

Theoretically, plasma volume can be determined by direct measurement (exsanguination), dilution method, indicator dilution method and bio-impedance (95-99). As this paper focuses on plasma volume measurement prior to and in human pregnancy, we limit our description to indicator dilution technique and bio-impedance.

Indicator dilution technique

Opposite to estimation of plasma volume by dilution of the circulatory content, indicator dilution techniques are based on administration of molecules that will be distributed over the circulation. These injected recognizable substances preferably have large molecular weight in order to (1) remain in the circulation throughout the measurement without affecting vessel integrity, (2) have minimal

first order disappearance by a combined loss binding, disintegration, degradation or renal excretion, (3) have well-known metabolisation and excreting pathways with acceptable half-life, and (4) neither pass nor being metabolized by the placenta, ensuring safety for the developing foetus.

With any indicator dilution method, the volume of blood plasma is calculated according to the following equation:

$$Volume_{Plasma}\ x\ concentration\ marker_{t=0} = Volume_{Injected\ dye}\ x\ concentration\ marker_{Injected\ dye}$$

In order to assess the concentration of the injected marker in the circulation at virtual t=0, a first order disappearance kinetic is assumed, allowing the dye to distribute over the circulation. Log transformation of the measured dye concentrations at given time points is performed, followed by a regression analysis in which the concentration of the dye at virtual t=0 can be assessed by the intercept of the y axis at t=0. Instead of assuming a mean escape rate, by using multiple time points after injection of the dye, the individuals' escape rate is taken into account, a method which largely compensates for caveats as mentioned above (amongst capillary leakage that comes with preeclamptic gestation) to overestimate plasma volume.

Plasma volume can be affected by numerous exogenous factors, such as sodium intake, exercise, fluid intake, and antihypertensives. In research, to reduce differences in observations between groups, one should take these confounders into account and monitor sodium output and use of antihypertensives to ascertain possible differences not to originate from dietary or medication effect.

Indicators

The last decades, different albumin-binding indicators have been used to measure plasma volume. T-1825 or Evans Blue is an azo dye which has a very high affinity for human serum albumin, and this was the most used plasma indicator dilution marker until the use of radioisotopes was developed. The greatest challenge in measuring Evans Blue concentration is its variable absorbance in turbid

plasma. Theoretically, determination of the dye concentration with the spectrophotometer at 620 nm would overcome most errors despite turbidity of plasma, residual dye in repeated determinations and haemolysis of samples (100). Nonetheless, comparison of different analytical strategies in determination of plasma volume using Evans Blue dye revealed no significant differences among the mean plasma volumes obtained with any method in pregnant women (100). Also the intra- and inter-assay coefficients of variation were comparably low (<2.8%) irrespective of the method employed (100).

Indocyanine green (cardio-green), another colour-dye, has also been used for determining plasma volume. Measurements correlate well with Evans Blue (correlation coefficient r=0.98), however it is known to be less stable, as it is eliminated by the liver with a plasma half-life of only 3 minutes (101). Multiple adverse reactions, especially in patients with iodide sensitivity, troubled a universal application of this dye.

Later, ^{131}iodide (half-life 8d) and ^{125}iodide (half-life 60d) have been developed as radioactive tracers and are used as albumin markers. This overcomes the overestimation of plasma fluid seen in dye-albumin measurements in some specific clinical conditions of increased transcapillary leakage like oedema, ascites or proteinuria. Therefore, the International Committee for Standardization in Haematology (ICSH) described radioiodine-labelled human serum albumin as a plasma label as the most reliable and reproducible technique for measuring plasma volume (102). With this indicator dilution technique, the labelled albumin is injected, and from a contralateral vessel, different venous blood samples are collected: one sample before the injection (t=0), and multiple samples at an exact time interval after the injection. Due to the known clearance rate, an exact plasma volume can be derived from the concentration in the blood samples.

Different studies report comparable results between plasma volume determination with Evans Blue and I-labelled albumin. Mean plasma volume determined by Evans Blue dilution did not differ significantly from that determined by ^{125}I-Human serum albumin in either clear or turbid samples (8).

In addition, both I-isotopes perform comparably in assessment of plasma volume and transcapillary permeability (103).

Notwithstanding radioiodine-labelled human serum albumin is seen as the gold standard, radioactive substances better be avoided during pregnancy. Therefore, high-molecular weight dextran may represent an attractive alternative to measure plasma volume as it seems to combine the advantages of ^{125}I-labeled albumin (a long half-life and a distribution space which is less susceptible for trans capillary leakage) with those of the dyes (non-radioactivity).

Dextran-70 can be quantitated by enzymatic determination of glucose, the only degradation product after hydrolysis, and has different advantages for the use during pregnancy: as dextran is relatively rapidly cleared from the plasma, consecutive measurements are possible (104). Moreover, the disappearance rate of dextran makes it possible to calculate the capillary leakage (105). This might be of potential interest in hypertensive gestational complications such as preeclampsia.

Next to the systematic error of about 50mL larger distribution space compared to ^{125}I-albumine, good correlations between detran-70 and ^{125}I-albumine in non-pregnant subjects has been found: the mean difference in plasma volume measured with the two indicators was 6% with an error of 5% in the plasma measurements with dextran-70 (105). There is one draw-back; Dextrans may induce anaphylaxis. The used dose to measure plasma volume is 20cc, which is considered a test dose to rule out hypersensitivity reactions in general practice. In case of hypersensitivity, at this dosage, only mild primarily pulmonary responses (wheezing) have been described.

Although radio-iodinated serum albumin is recommended, there are numerous other labelled proteins successfully used to measure plasma volume in humans. ^{59}FE-labelled transferrin has been investigated because of its lower cost against iodine. It has been suggested that the reliability of ^{59}FE-labelled transferrin in comparison with iodinated human serum albumin may be less and depend on iron saturation (and with it first order disappearance kinetics), affecting the fractional clearance rate, which is in general faster than ^{125}I, but especially so in iron deficiency (106, 107).

Hydroxyethyl starch (HES) is a colloid with high in vitro molecular weight (130 kDa), but with a still high in vivo weight (70-80 kDa). It consists of glucose and hydroxyethyl glucose that are interconnected by α–glycosidic bondings. Using HES as a dilution marker was first proposed in 1997 (108). The HES method for plasma volume estimation is found to be rapid, safe, well tolerated and acceptable for use in pregnant women, as it does not cross the placenta (109, 110). Unlike the other dilution methods which are based on the dilution of a known quantity of the indicator, plasma volume measurements using HES is based on the increase in plasma glucose concentration after acid hydrolysis (111, 112). Complete hydrolysis of HES disrupts the α–glycosidic bonds and produces glucose and hydroxyethyl glucose resulting in a fixed concentration of glucose, which does not change by extending the hydrolysis process. Therefore, the difference of glucose concentration before and after the injection with HES is proportional with the HES concentration in the plasma (Δ glucose ≈ $concentration_{HES}$), which is proportional to the quotient of the HES volume injected and the plasma volume ($concentration_{HES} \approx volume_{HES}$ /plasma volume). This results in the following equation:

$$\Delta\ Glucose = k\ x\ \frac{Volume_{HES}}{Plasma\ volume}$$

With k found to be a constant factor of 3082mg%[105]. From this, plasma volume can be calculated as:

$$Plasma\ volume\ (mL) = \frac{3082\ x\ Volume_{HES}}{\Delta\ Glucose}$$

It is unclear whether this technique can be used after HES has been infused for plasma expansion.

Bioelectrical impedance analysis (BIA)

A different approach to determine body fluid content is bioelectrical impedance analysis (BIA). BIA allows the calculation of body composition and volumes by analysing the changes in frequency [Hz] of an electric input voltage signal traveling through the body. After applying electrodes on hand and foot, an alternating current flows through physiological fluids of the body by the movement of ions, passing capacitive and resistive elements. Because water and electrolytes are the determinants of

electrical conduction in the body, body fluid content can be evaluated by the BIA-technique. In this, the current flows primarily in the extracellular space at low frequencies, whereas at high frequencies the current flows through intercellular space and extracellular volumes.

In the BIA assessment, several arithmetical assumptions are made: first, the human body is considered a cylinder consisting of different smaller cylinders (arms, legs and thorax) and second, body composition is supposed homogenous. With respect to fluid content, BIA estimates total body water as the sum of intracellular water and extracellular water. The latter consist of interstitial, transcellular- and plasma volume.

Different studies have validated the reliability of total body water, intra- and extracellular water using a bioimpedance technique (108, 113). They showed that multi-frequency impedance is able to acceptably estimate body water volume, when compared to dilution methods (113).

Whereas the classic methods for plasma volume assessment are expensive and not easy to employ for clinical use, BIA method is simple and safe. However, some concerns regarding the validity of BIA in pregnant women are made, with respect to the above-mentioned assumptions. A homogenous body composition is not always true for critically ill patients or pregnant women. Full body bioelectrical impedance measurements might be influenced by the amniotic fluid and the foetus when analysing the 'maternal' body composition. Moreover, although plasma volume and extra cellular volume relate to each other, oedema formation might alter this relation (114, 115).

The increase of total body water and extracellular water volume in normal pregnancies measured with the BIA technique has been reported extensively (114, 116). As plasma volume is proven to be increased during pregnancy, one may conclude that the measured augmentation of total body water and extracellular water implies an increase of plasma volume. Concurrent measurement of plasma volume along with BIA during pregnancy has not been done so far.

Therefore, BIA technique may be a useful technique to estimate intracellular and extracellular water, but is currently not considered suitable to distinguish between intra- and extravascular fluid in pregnancy.

5. RECOMMENDATIONS

In human cardiovascular physiology, the venous compartment and volume homeostasis play a much more important role than generally considered today. Even more, during pregnancy the physiological properties of both systems are unequivocally needed for achieving the high flow/low resistance circulation required for optimal maternal – fetal exchange at the placental site. In order to better understand normal and pathological adaptations of maternal hemodynamics, it is important to include veins and volume in hemodynamics studies, together with all other aspects and sites of the circulation.

Current findings on maternal venous hemodynamic function obtained by Doppler sonography are interesting, but require confirmation by data obtained via other research methods, such as animal- or lab- experiments, clinical observations and epidemiologic studies.

Research technologies to investigate venous hemodynamics during pregnancy are scarce and today, only ultrasonographic Doppler assessment seems applicable for this purpose. There is a strong need to explore and validate more non-invasive methods to investigate gestational venous hemodynamics.

Knowledge of the plasma volume in the preconceptional phase is useful for individual risk estimation for (recurrent) gestational hypertensive disease, and may also guide preconception life style recommendations.

Currently, the best dye for plasma volume measurement in non-pregnant conditions is still radioiodine-labelled human serum albumin, but other large molecular weight indicators as Hydroxyethyl starch (HES) are good substitutes that can also be used to monitor gestational plasma volume status.

New techniques based on impedance analysis are promising tools for body fluid estimation during pregnancy, however comparative studies with established techniques for plasma volume measurement are lacking today.

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Figure 1 The shapes of venous Doppler flow waves represent a spectrum, of which the two extremes - as commonly seen at the level of hepatic veins - are presented here: a flat pattern on the left, and a triphasic pattern on the right. The latter shows typical deflections related to the phase of the cardiac cycle in the right atrium: X represents forward (cardiopetal) flow following atrial diastole, V represent decelerating forward flow at filling of the atrium with closed tricuspid valve, Y represents forward flow resulting from ventricular diastole with opened tricuspid valve and A represents reversed (cardiofugal) venous flow backwards into the venous system following atrial systole. The time interval between ECG P-wave and Doppler A-wave can be measured as the Venous Pulse Transit Time.

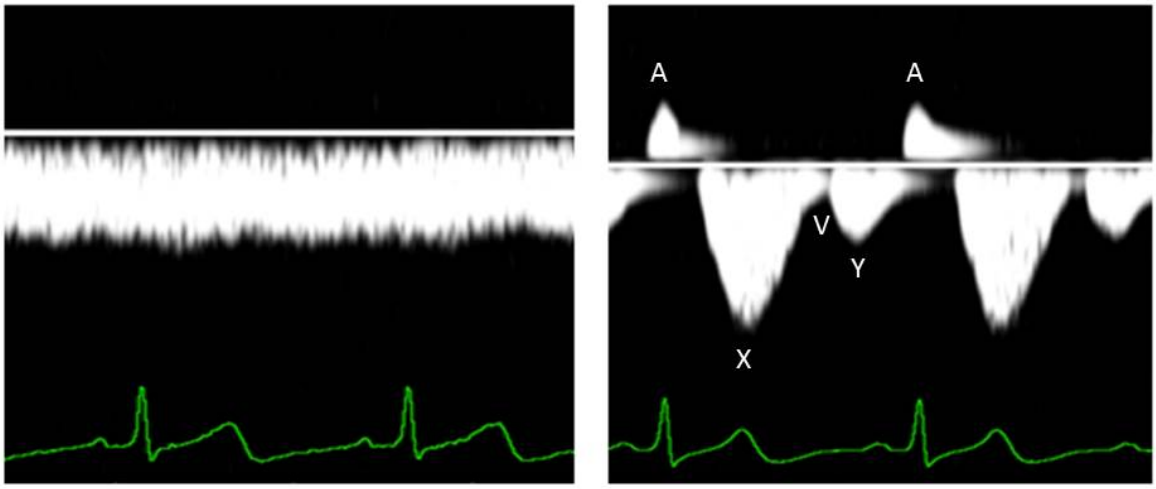

Figure 2. Venous pulse transit time (VPTT 5th, 50th and 95thpercentile) changes from early pregnancy until term, as measured at the level of the hepatic veins (adopted and redrawn from 67). VPTT is defined as the time interval between ECG P-wave and Doppler A-wave in msec (Figure 1), relative to the duration of the cardiac cycle in msec (time interval between 2 consecutive ECG R-waves). Similar to pulse transit time at the arterial site, VPTT is considered a measure for venous vascular tone.

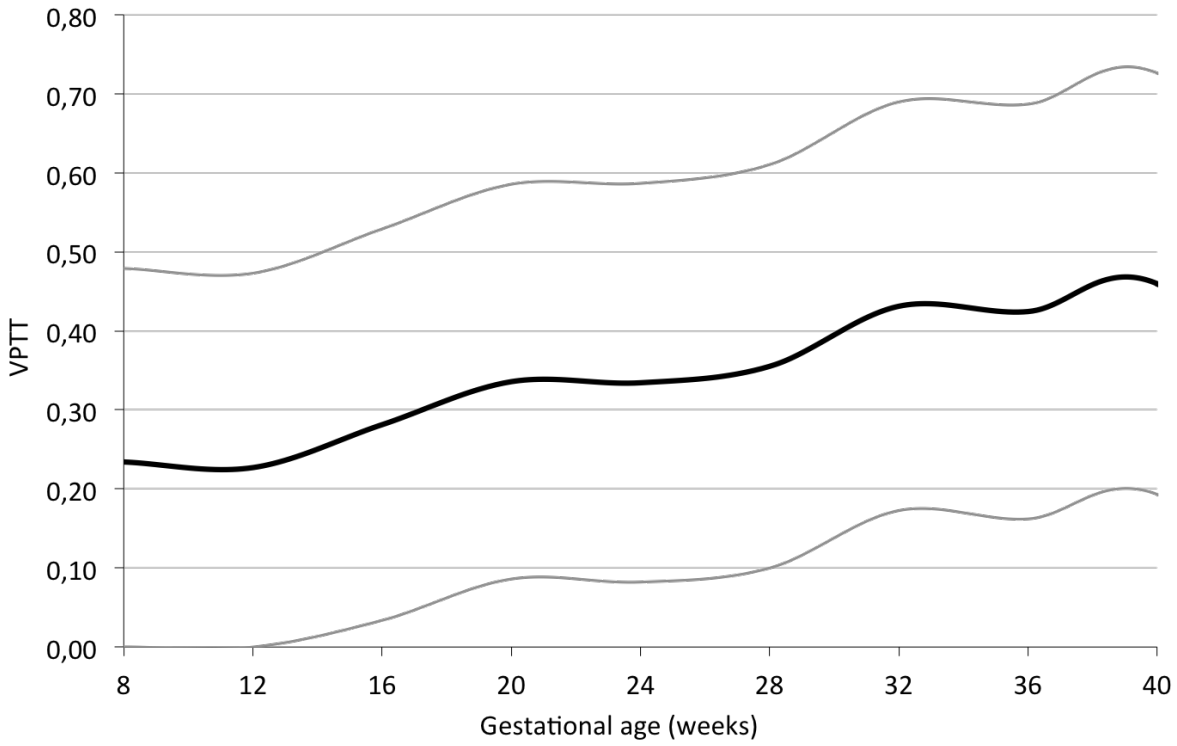

Figure 3. Plasma volume (L) (5^{th}, 50^{th} and 95^{th}percentile) changes from non-pregnant until 40 week gestational age. (adopted and redrawn from 75)

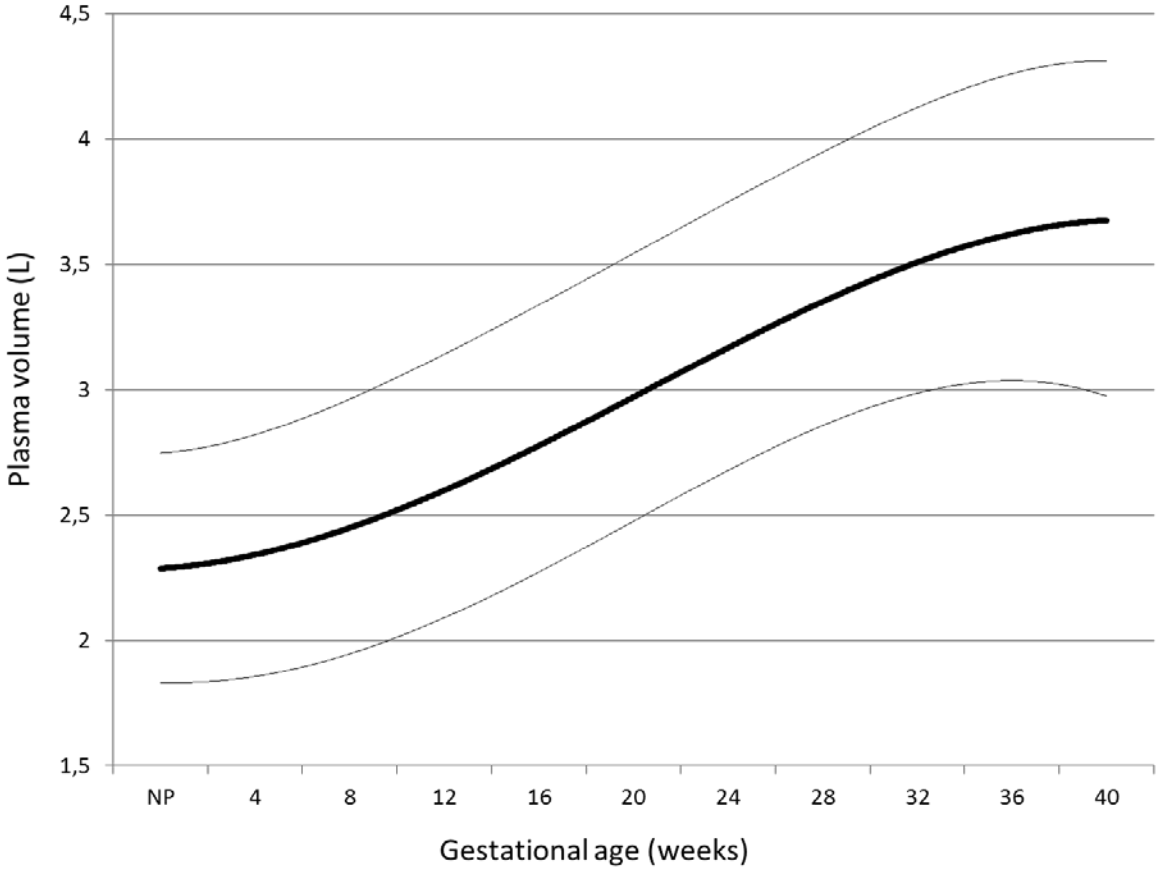

Figure 4. Illustration of positioning the ultrasound probe for venous Doppler flow assessment at the level of hepatic veins and renal interlobar veins, as reported elsewhere (16)(33).