The role of intra abdominal hypertension and maternal venous compartment in the pathophysiology of preeclampsia

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ABSTRACT

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The incidence of preeclampsia in the western countries is estimated to range from 2% to 6% in healthy, nulliparous women. In developing nations, the incidence of the disease is reported to be 4- 18%, with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries Etiology of the disease is multifactorial, with risk factors like maternal age, oxidative stress, angiotensin T-235 homozygote having a different role in every case. Moreover, the disease its self is a multisystem expression of a complicated pathophysiology. Many attempts to explain the latter have been made with often controversial results. In the present article we explore the hypothesis of intra-abdominal pressure as possible causative factor of preeclampsia and the role of the maternal venous compartment and rennin-angiotensin-anldosterin system in this hypothesis

INTRODUCTION

Preeclampsia is a multisystem disorder that complicates 2-8 % of pregnancies and together with the other hypertensive disorders of pregnancy contributes significantly to perinatal mortality and morbidity[1]. Preeclampsia is defined as the presence of hypertension (Blood Pressure BP≥140/90 mm Hg) on 2 occasions, at least 6 hours apart, but without evidence of end-organ damage, in a woman who was normotensive before 20 weeks' gestation and proteinuria (>0.3gr/24h). In a patient with preexisting es-

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sential hypertension, preeclampsia is diagnosed if systolic BP (SBP) has increased by 30 mmHg or if diastolic BP (DBP) has increased by 15 mmHg. Depending on the severity, symptomatology may also include pulmonary oedema, cyanosis, visual disturbances, epigastric pain, persistent headaches, intrauterine fetal growth retardation (IUGR), e.t.c[2]. Pathogenesis of the disease is multifactorial. Various risk factors have been mentioned in the literature, each with different effect: nulliparity (odds 3:1), family history(5:1), maternal age>40 (3:1), diabetes mellitus (2:1), chronic hypertension (10:1), chronic renal disease (20:1), homozygosity and heterozygosity for angiotensinogen gene T235 (odds 20:1 and 4:1 respectively), antiphospholipid syndrome (10:1), and others[2]. In the present article we explore the hypothesis of intra-abdominal pressure (IAP) as possible causative factor of preeclampsia and the role of the maternal venous compartment and rennin-angiotensin-anldosterin system in this hypothesis.

THE PROOFS

It's almost a century ago that H. Paramore suggested that preeclampsia is a secondary result of intra-abdominal hypertension[3]. Today, there is more evidence to support this thesis.

Animal studies report that increased IAP may be a cause for systemic hypertension in central obesity and preeclampsia[4]. Raised IAP has also been measured postpartum in healthy women, immediate after caesarian section; while under spinal anesthesia, intra-abdominal pressure in >25% of healthy term parturients was > 12 mmHg[6]. The two syndromes also share a lot of clinical signs like arterial hypertension, oedema, proteinuria, headaches and nausea[7].

Apart from that, maternal endothelial dysfunction in preeclampsia is associated with increased soluble fms-like tyrosine kinase-1 (sFlt-1), a circulating antagonist of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). Angiotensin II (AT II) is a potent vasoconstrictor that increases concomitant with sFlt-1 during pregnancy and may promote the expression of sFlt-1 in pregnancy. In other words, elevated sFlt-1 levels in preeclampsia may be caused by a dysregulation of the local rennin/angiotensin system (RAAS) [9-11]. Plasma rennin activity (PRA) and concentration (PRC), and plasma AT II and aldosterone concentrateons (PAC) are reduced compared to normal pregnancy[12]. In the second case and relatively to PRC and ATII, pro-rennin is more increased[12-14]. In preeclampsia pro-rennin remains increased[13-14]; that, could explain arterial hypertension. Recently, investigators have located Angiotensin-(1-7) which has vasodilatating and natriuretic properties related with aquaporin-1[14-16]. The balance between the two- results

in the expression of vasoconstrictor and volemic effect in every physiological function.

During an uncomplicated pregnancy, estrogen leads to increased angiotensinogen synthesis by the liver leading to increased AT II. Yet, there is concomitant reduction in vascular sensitivity to endogen AT II[15]. In fact, pregnant women require twice as much AT II by intravenous infusion as compared with their non pregnant counterparts to achieve similar vasomotor responses[8]. In preeclampsia, there seems to be an increased sensitivity to AT II administration[17-19]. Even though concentration of AT II and Angiotensin-(1-7) are relatively low, hypertensive response could be explained by imbalance between the two subastances[20,21]. On the other hand, AT II vascular sensitivity may be inhibited during normal pregnancy but adrenergic response is normal; as a result plasma aldosterone is increased and volemic effect exists (marked expansion of the extracellular volume and the plasma volume)[22,23]. In preeclampsia, aldosterone levels are low, often due to defect in 18-methyl oxidase activity which leads to impaired aldosterone synthase activety[24]. Along with that, rennin and AT II levels commonly decrease toward the normal nonpregnant range. This means that preeclampsia-compared to normal pregnancy- is a status of increased vascular contraction with concomitant endovascular volume depletion. Moreover: the combination of hypertension and "normal" levels of rennin and AT II can be seen as an indication of a hyperactive RAAS. They are in fact what one would expect from a self-regulating system: if hypertension was caused by a factor outside the system, the RAAS should have turned itself down (i.e. lower AT II and rennin levels).

The aforementioned may also explain the normal plasma rennin levels in chronic intra-abdominal hypertension[4].

Some investigators have focused on other mechanisms linked with the role of the RAS in preeclampsia, e.g AT II type 1 receptor agonistic auto antibodies, AT1-B2 hetrodimerization, uteroplacental rennin secretion and a redox switch in angiotensinogen[26-28]. In some cases (e.g. AT II type 1 receptor agonistic auto antibodyes) the importance of local RAAS in the uteroplacental unit (found in cytotrophoblast, decidua and placental endothelium) is also highlighted[29].

Others studied the maternal venous compartment. The splanchnic bed is the main blood reservoir of the body, containing up to 25% of total blood volume[30]. The vascular histological structure within it, contributes actively to the regulation of cardiac output, through active venules' vasoconstriction and passive "emptying" of venous reservoir after arterial vasoconstriction[30-32]. Venous hemodynamic disturbances cause organ injury mainly through 1) increase intravenous pressure which leads to ve-

nous stasis at microcirculation and 2) impaired tissue perfusion due to arterial vasoconstriction[32].

During pregnancy, it appears that venous adaptations favor a pro-vasodilatory state in which α-adrenergic responsiveness is decreased, coupled with an increase in endothelial-dependent vasodilatatory responsiveness which appears to be primarily mediated by an nitric oxide (NO)-dependent mechanism. In addition, there is downregulation of smooth muscle response to NO which is largely related to cGMP production and this is likely compensated for by large increases in NO production and/or availability. The increased capacitance of the venous system is necessary to accommodate the plasma volume increases seen in normal pregnancy[31-35]. A dilatation of the left atrium occurs already in early gestation, whereas a rise of atrial natriuretic peptide (ANP) is observed in the second half of pregnancy. This rise of ANP originates from extension of the atrium due to expansion of the plasma volume and prevents overfilling of the cardiovascular system[33-34].

Preeclampsia, on the contrary, is known as a maternal cardiovascular maladaptation syndrome. Venous distensibility, capacitance, and compliance are reduced. In pregnant women who subsequently develop early-onset preeclampsia, first trimester cardiac output is lower than normal, whereas this is higher than normal in women destined to develop late-onset preeclampsia. Arterial hypertension and liver and/or renal dysfunction can be secondary to abnormal venous hemodynamics[35-36].

Doppler ultrasonography shows promising results with respect to evaluation of maternal cardiovascular maladaptation. In non-pregnant individuals, Doppler studies of renal interlobar veins are used in obstructive uropathy to distinguish physiological from pathological pyelocaliectasis, for non-invasive monitoring of transplant kidneys and in the work up of renal vein occlusion[37-38]. During pregnancy, studies are mainly focusing on hepatic (HV) and interlobar renal veins. During the course of normal pregnancy, the HV waveforms changed from predominantly triphasic to predominantly monophasic patterns, even though inter- and intra-individual variation have also been described. Along with that impendance index of renal interlobar veins (RIVI) decreases during the course of pregancy and this is consistent with an increase of venous compliance[38]. That is: the gestational decrease in renal interlobar vein (RIV) impedance index (RIVI) and flattening of the hepatic vein (HV) waveform correlate well with the known reduction in peripheral vascular resistance and the increased intravascular blood volume during pregnancy[37-39]. RIVI is higher in preeclampsia than in uncomplicated pregnancies[24]. Moreover, RIVI is higher in early preeclampsia than in late preeclampsia pregnancies and this is associated with lower

birthweight percentiles and higher proteinria[40]. Higher RIVI was also associated with a sharp reduction in forward venous flow during the last 100 ms of the Doppler wave; the latter being result from venous preacceleration nadir (VPAN) mechanism, i.e backflow of atrial blood into the venous system during atrial contraction, by lack of a valve mechanism[39].

HYPOTHESES AND PERSPECTIVES

If we combine the aforementioned, we reach the recent reframing of the hypothesis of the pathogenesis of preeclampsia. According the latter, raised IAP during pregnancy can cause compression of renal veins. Ultrasonographic data provide evidence for impaired drainage of venous blood from the kidneys during preeclamptic pregnancy. This reduction in renal perfusion will activate the RAAS through the juxtaglomular apparatus[41-44]. Activation of RAAS will have many effects including increased rennin secretion, increased reabsorption of sodium and fluid, arteriolar vasoconstriction and a rise of blood pressure[7]. Yet, the fact that these phenomena are not fully noticed during preeclampsia may be explained by the fact that RAAS is inhibited during clinical phase of preeclampsia but not during initiative phase[42-44]. The consistency of reduced renal perfusion, will lead to a constant RAAS activation in order to restore renal blood flow. This could provoke a raise in angiotensin II (AT II) and alterations of the levels of molecules like VEGF, PIGF and fms-like tyrosıne kinase-1; changes which could cause maternal endothelial dysfunction and give rise to many symptoms of preeclampsia[41-43].

Furthermore, in certain conditions (e.g. obese women), raised IAP could induce a status of decreased cerebral venous outflow to such degree that it could create a raised ICP situation (pseudotumor cerebri). The latter is known to predispose for other obstetric complications, such as placental abruption[46].

Yet, if the compression theory of renal veins due to raised IAP is proven to be correct, then other questions arise. For example, further research is needed to prove whether in the pathophysiology of preeclampsia participate other abdominal vessels (e.g. uterine veins), or whether it's the compression of one or both renal veins – and in what degree- that triggers the pathologic sequence. It would also be interesting to study the influence of different body positions in women with preeclampsia, while looking at the renal veins resistance or compression, the rennin and AT II levels and the blood pressure at the same time[41]. Monitoring and studying local RAAS (especially in uteroplacental unit) should also give us new information on the subject.

The acceptance of the theory may create new therapeutic approaches. Simple measures like

not lying on their back when being at risk of preeclampsia should probably be advised in these patients. And if that's not enough, elective stenting of the renal veins could also be a therapy option.

Additionally, the fact that 38% of cases with seizures (eclampsia) occur before labor, 18% during labor and 44% (usually 24-48h) after labor, implies that the removal of the source of raised IAP (fetus) is not enough to stop the pathophysiological sequence in all cases. Is the pharmacological inhibition of RAAS–most likely at AT II level, but without excluding the rest of the possibilities,e.g. Angiotensin-(1-7) or Angiotensin-(1-5)–a feasible treatment option in certain patients?

Effect of anesthesia and analgesia is under question too. In experimental modest epidural anesthesia seems to lower proteinuria and SBP[47-48].

And if understanding of IAH in maternal care is limited, it is completely unknown whether there are subclinical effects of even modest elevations of maternal IAP on the fetus. In animal models intra-amniotic pressure (IAMNP) has been related linearly to maternal IAP[49]. Some investigators hypothesized that elevated IAMNP is translated to elevated fetal IAP, both of which were vulnerable to elevations in maternal IAP. Through this mechanism, elevated fetal IAP could result in increased urethral resistance, the chronicity of which could lead to abnormal development of the bladder detrusor muscles, resultant dysfunctional voiding in children and possible urinary tract anomalies. But this question is still under investigation[50].

CONCLUSION

The information summarised above reveals a new and tempting hypothesis: the clinical stage of preeclampsia, a condition generally considered as one of the most serious gestational complications of which background mechanisms are not yet fully understood, might be a systemic response to a combination of intra-abdominal hypertension with a preceding failure of the venous system to regulate cardiac output appropriately. In order to accept or refute this hypothesis, data from more studies and observations are needed. This is why the exploration of the adult's venous compartment, RAAS and intra-abdominal pressure both in non-pregnant and pregnant conditions, is of interest to all and scientists involved in research and management on gestation-induced maternal disturbances.

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Author Disclosures:

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