International Journal of Gynecology & Clinical Practices
Expert Opinion Open Access

Suggestion for a Modified Classification of Hypertension during Pregnancy

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Publication History:

Received: December 13, 2019
Accepted: February 15, 2020
Published: February 17, 2020

Keywords:

Hypertension in pregnancy, Modified classification

The history of preeclampsia research is full of contradictory findings. Classic hemodynamic examinations revealed low cardiac output (blood volume) and severe vasoconstriction [1,2]; however, others reported a hyperdynamic condition with high cardiac output in preeclamptic women [3]. Similar controversy was found in cerebral flow in patients with serious preeclampsia, as both decreased and increased perfusion occurred [4]. Placental insufficiency with fetal growth restriction is a hallmark of preeclampsia [5]. In contrast, statistical data clearly demonstrated that not only low but high fetal birth weight as well is more frequent in patients admitted with the diagnosis of preeclampsia than it is in healthy pregnancies [6].

Since 2003, in scientific articles preeclamptic cases have been frequently distinguished as *early-and late-onset preeclampsia*, according to the gestational age when clinical onset of the disease appears; before the 34th week or later, retrospectively [7]. This kind of distinction is highly indicated since the outcome of preeclamptic pregnancies is markedly influenced by the gestational age when clinical symptoms appear; much better in late-onset cases. However, this kind of preeclampsia separation considers the gestational age when classical symptoms are detected but not the pathophysiological differences between the two subtypes. Up to date, accumulating data demonstrate that gestational hypertension with organ failure, denominated as preeclampsia, can develop via different pathways [8-12].

Gestational Hypovolemic Hypertension and Preeclampsia

This kind of preeclampsia characteristically develops in young primiparous women. The progenitor of placental pathology is most probably an immunological imbalance between the maternal immune system and the semi-allograft embryo; the placentation is already diminished by the very early gestation [13]. The high levels of anti-angiogenic proteins (soluble Fms-like tyrosine kinase, soluble Endoglin) interfere with normal placental development. Agents from this under-perfused placenta enter the maternal circulation and damage the endothelial cells. The resulting acute inflammation-like *atherosis* initiates the clinical manifestation of the disease. Damaged endothelial cells produce less vasorelaxant agents such as nitric oxide (NO), Prostacyclin (PGI2), and Endothelium-derived Hyperpolarizing Factor (EDHF), but release Endothelin 1 (ET-1), a potent vasoconstrictor. The hypertension in early-onset preeclampsia is caused by vasoconstriction; the blood volume is contracted, determined as low cardiac output [1,14].

The other important consequence of endothelial damage is platelet activation [15]. Activated platelets, releasing thromboxane A_2, (TXA_2), another vasoconstrictor, adhere to the damaged vessel walls. This phenomenon results a crucial consequence at the level of microcirculation. The endothelial edema with platelet adhesion can critically narrow the capillary diameter which is already originally narrower than the diameter of erythrocytes. Entrapped red blood cells form capillary *microthrombi* [16,17]. Some erythrocytes sustain a break (*peripheral mechanical hemolysis*) and release adenosine diphosphate (ADP) which causes further platelet activation. The increasing number of plugged capillaries basically determines vascular resistance and obviously decline tissue oxygenation. Early and easily detectable sign of the organ deterioration is *proteinuria*.

In the early stage of this process, increasing blood pressure seems to be beneficial to maintain tissue perfusion (perfusion = pressure/resistance). By further progression, even the higher pressure cannot overcome the increasing resistance and signs of organ failure(s) appear. In the terminal stage of this condition, capillary hypoxia leads to vascular transparency [18], resulting in generalized edema and terminal organ failures, such as oligo-anuria or eclampsia.

This type of preeclampsia is considerably appropriate for the placental-originating *early-onset preeclampsia*.

Gestational Hypervolemic Edema, Hypertension, and Preeclampsia

Enhanced Na^+ and water retention, as an initiator of gestational hypertension or preeclampsia, was already considered in 1991 [19]. In accordance with this, contrary to the characteristics of early-onset preeclampsia, high cardiac output and increased fetal birth weight were also reported in pre-eclamptic patients [3,6].This condition seems to be appropriate for *late-onset preeclampsia*, in which the high maternal pre-pregnancy weight, and increased gestational weight gain are characteristic features.

Extremely augmented water retention can genuinely explain the edema, the blood pressure elevation, the ascites, and, due to organ' edema, also organ failures, such as proteinuria, fetal hypoxia or even eclampsia.

Obesity seems to be a risk factor for hypervolemic gestational pathologies. Obesity is known to be associated with increased pulse rate and increased circulating blood volume [20]. Blood viscosity is

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Citation: Tamás P, Koppán M (2020) Suggestion for a Modified Classification of Hypertension during Pregnancy. Int J Gynecol Clin Pract 7: 152. https://doi.org/10.15344/2394-4986/2020/152

also elevated by higher levels of plasminogen activator inhibitor 1 (PAI-1), released from adipocytes [20]. Angiotensinogen, released also from adipocytes, possesses a vasoconstrictor effect and augments water retention [21,22]. In an insulin resistance condition, which is also characteristic to obesity, high insulin levels enhance renal salt retention, further elevating blood volume [23].

Concordant with the pathological role of extremely increased water retention, the decrease of cardiac output by the use of diuretics results in a parallel decrease of blood pressure [24]. It seems the water excretion cannot balance the 2 liters of normal gestational, and the obesity-induced water retention in such cases.

In this type of preeclampsia the first sign, in accordance with wide clinical experiences, the edema which always antedates hypertension and hypertension usually antedates the proteinuria.

Summarizing these data, basically *two main types of preeclampsia* can be distinguished, when a marked difference between the two types is vascular condition, and consequently, the blood volume.

Hypovolemic preeclampsia; characterized by contracted blood volume, vasoconstriction, generalized microthrombosis; a severe and quickly progressing condition with fetal compromise, such as growth restriction, oligohydramnios, and hypoxia. Clinical symptoms appear mostly during late second or early third trimester. In laboratory markers, decreasing platelet count, increasing lactate dehydrogenase (LDH) enzyme, and transaminase levels are characteristic findings; proteinuria is marked and increasing. The first sign is hypertension, followed by proteinuria and, in the terminal phase, by generalized edema, placental abruption or eclampsia.

Hypervolemic preeclampsia; characterized by high pre-pregnancy weight, increased gestational weight gain, generalized edema, and normal weight's or larger fetus. Laboratory alterations, including proteinuria, are modest; platelet count remains within the normal range. The first sign of this pathology is leg edema which will turn to a generalized form, detected also as increasing weight gain. Further water retention can elevate blood pressure. In some cases, ascites and proteinuria will also appear, probably due to tissue edema. This kind of marked interstitial fluid accumulation can lead to serious clinical signs of placental and cerebral deteriorations, resulting acute fetal hypoxia, placental abruption or eclampsia.

Classification of Hypertension during Pregnancy

One of the recent classifications of hypertension during pregnancy distinguishes:

1. Chronic hypertension
2. Gestational hypertension
3. Preeclampsia: gestational hypertension with proteinuria or with other maternal organ or uteroplacental dysfunctions [25]

The earlier classification *quantitatively* differentiated preeclampsia as mild or severe, depending on values of blood pressure and/or proteinuria.

By this time, several data have already accumulated to support modification of preeclampsia classification. Based on these new findings of preeclampsia research, and also on broad clinical experiences, we aspired to collect a modified classification of hypertension in pregnancy, distinguishing preeclampsia types *qualitatively*.

Gestational Hypovolemic Hypertension & Preeclampsia

1.1 Compensated stage: gestational hypertension only

1.1 a/ platelet count > 150 x 10^9/L
1.1 b/ platelet count ≤150 x 10^9/L

1.2 Decompensated stage: hypertension + sign(s) of organ dysfunction

1.2 a/ Estimated fetal weight > 10 pct.
1.2 b/ Fetal growth restriction and/or oligohydramnios
1.2 c/ Fetal distress

1.3 Terminal stage: hypertension + sign(s) of organ dysfunction + generalized edema

1.3 a/ No fetal distress
1.3 b/ Fetal distress
1.3 c/ Placental abruption or eclampsia

Gestational Hypervolemic Edema, Hypertension & Preeclampsia

2.1 Gestational edema

2.1 a/ Lower-extremity edema
2/1 b/ Generalized edema

2.2 Gestational edema + hypertension

2.3 Hypervolemic preeclampsia: gestational edema + hypertension + proteinuria

2.3 a/ No fetal distress
2.3 b/ Fetal distress
2.3 c/ Placental abruption or eclampsia

Superimposed Preeclampsia

Hypertension + sign(s) of organ dysfunction(s) with (known) disease(s) associated with thrombophilia, endothelial damage, or renal/liver disease

3.1 Clinical onset at or after 34th week

3.1 a/ No fetal involvement
3.1 b/ Fetal involvement

3.2 Clinical onset before 34th week

3.2 a/ No fetal involvement
3.2 b/ Fetal involvement

3.3 Placental abruption or eclampsia

Chronic Hypertension

Hypertension known before conception or diagnosed before the 20th gestational week.

We hope, this clinically-induced classification generates scientific debates and promotes the development of a new, widely acceptable classification of hypertension during pregnancy.

Competing Interests

The authors declare that they have no competing interests.

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