HYPERTENSIVE CONDITIONS DURING PREGNANCY. A MODERN VIEW OF THE PROBLEM. (LITERATURE REVIEW)

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https://doi.org/10.5281/zenodo.11409638

Abstract*. Hypertensive conditions in pregnant women remain a major cause of maternal and neonatal pregnancy-related morbidity and mortality worldwide. Affected women are also at increased risk of cardiovascular disease in later life, independent of traditional cardiovascular risks. This article analyzes the current literature on the etiology and pathogenesis of these complications.*

Keywords*: hypertension, preeclampsia, marker.*

Hypertension is the most common condition of pregnant women and has been reported to complicate up to 1 in 10 pregnancies and affects approximately 240,000 women in the United States each year [1]. Although physicians have recognized this problem as an acute problem for millennia, relatively little is known about its pathogenesis and prevention. The main problem with high blood pressure is related to its potential harmful effects on both the mother and the fetus. These potential side effects range in severity from minor to life-threatening.

During pregnancy, dramatic physiologic changes occur in systemic hemodynamics. It is very important to consider these differences from the non-pregnant woman when attempting to assess blood pressure during pregnancy. In uncomplicated pregnancy, mean arterial pressure falls, reaching its minimum between 16 and 20 weeks of gestation. The decrease in diastolic pressure is slightly greater than systolic pressure. The decrease is usually 8-10 mmHg or less than 10% compared to pre-pregnancy levels. The drop in blood pressure begins with the luteal phase of menstruation and progresses if it is followed by conception. After the 20th week, mean blood pressure slowly returns to pre-pregnancy levels around the 40th week of pregnancy. Circadian changes in blood pressure persist during pregnancy, as evidenced by ambulatory blood pressure monitoring.

Changes in systemic blood pressure are accompanied by changes in cardiac output, which increases dramatically. The peak is reached between the 16th and 20th weeks of pregnancy, and at the peak the increase is usually at least 40% greater than baseline. Both stroke volume and heart rate increase to achieve this significant increase in the amount of blood pumped into the pulmonary and great circle of circulation [3]. Increased volume loading of the heart results in left ventricular hypertrophy commensurate with the increase in cardiac work required to achieve the increase in cardiac output [4]. The decrease in mean arterial pressure becomes even more dramatic when viewed in the context of changes in cardiac output. Not only is cardiac output increased, but plasma volume is also significantly increased. This increased circulatory capacity with decreased tone has led to the vasculature described as sluggish during pregnancy. Decreased smooth muscle tone is not limited to the vasculature but is characteristic, for example, of the smooth muscles of the gastrointestinal tract and urinary tract.

Levels of circulating hormones that help regulate blood volume, especially all components of the renin-angiotensin-aldosterone system, as well as catecholamines, paradoxically increase

during pregnancy. The usual physiologic stimuli for the release of these hormones are decreased plasma volume or decreased renal perfusion. However, increased activity of the renin-angiotensin axis is a hallmark of the volume-increasing state during pregnancy. This has led to the description of pregnancy as a state of "decreased effective plasma volume". Increases in both arterial elasticity and venous capacity appear to underlie this unique physiologic phenomenon [3], the understanding of which remains enigmatic. As will be discussed later, it is the alteration of this pattern that characterizes the specific form of hypertension during pregnancy known as preeclampsia.

Changes in vascular reactivity are not limited to the response to endogenous hormones. The vasoconstrictive effect of administered pressor compounds is also significantly reduced. More than 40 years ago, the resistance of pregnant women to the pressor action of angiotensin II and norepinephrine during gestation was demonstrated [5, 6]. Subsequently, Gant et al. demonstrated a consistent increase in angiotensin II resistance as pregnancy progressed, peaking between 24-30 weeks of gestation [5, 9, 11, 17].

In healthy pregnant women, marked tubular hyperfiltration is observed. A rapidly developing increase in renal blood flow and glomerular filtration rate has been reported in rigorous human studies [8]. The SCF begins to increase in the first trimester of pregnancy and peaks in the second half of pregnancy, when it increases from normal levels for non-pregnant women by 40-60%. Davison and colleagues found that these improvements in renal hemodynamics occurred even before changes in cardiac output and plasma volume. This suggests that the mechanisms underlying these profound physiologic changes may be different, or at least not interdependent. There is no other case in biology where such a sustained improvement in function has occurred. The magnitude of the change has led many researchers to try to determine the mechanism underlying it so that it can be used to treat other human diseases. So far, no definitive explanation has been proven. If pregnancy remains uncomplicated, pregnant women with concomitant kidney disease usually show an improvement in function proportional to their baseline levels. The cause of the physiologic change is presumably teleologic and is designed to accommodate additional waste products resulting from enlargement of the uterus, placenta, and fetus. Although it tends to decrease toward the end of pregnancy, a significant increase in the glomerular filtration rate and renal plasma flow persists throughout pregnancy. The improvement in renal function is accompanied by reciprocal decreases in blood urea nitrogen and serum creatinine levels, commonly used to assess the rate of glomerular filtration. Low levels of these nitrogenous waste products in the blood are a sign of physiologic pregnancy. It is critical to consider these differences from normal values for nonpregnant women, as minor deviations from pregnancy levels may portend a diagnosis of preeclampsia. Throughout pregnancy, the average woman retains approximately 1000 mEq of sodium as she experiences a fairly steady increase in extracellular and plasma volume. Nevertheless, women experiencing a physiologic pregnancy will respond adequately to sodium restriction or sodium infusion [3].

It is difficult to study completely untreated preeclampsia, and often preeclampsia is diagnosed in patients with chronic conditions. Data from treated patients with preeclampsia or patients with pre-existing kidney disease, diabetes, or hypertension may not accurately reflect data from patients with uncomplicated preeclampsia. In addition to these concerns, available data suggest that systemic hemodynamic preeclampsia differs substantially from that in women with uncomplicated pregnancy.

Visser and Wallenburg performed a detailed hemodynamic evaluation of untreated first-pregnant women with preeclampsia. Using Swan-Ganz catheters, they consistently found cardiac output and intravascular volume to be lower, and systemic vascular resistance and cardiac afterload to be higher in these carefully selected groups of women with pregnancy-induced hypertension compared with normal pregnant control women [3].

If we focus on the properties of the arterial system in preeclampsia using impedance techniques, the pliability of the large conduit arteries is reduced. This suggests that the reservoir properties of the arterial system are impaired. Left ventricular muscle mass and diastolic pressure in the heart wall at late gestation are similar in subjects with preeclampsia and controls. However, limited data suggest that left ventricular contractility in preeclampsia is inadequately low given the high afterload [3].

Some changes in the systemic hemodynamics of pregnant women with a predisposition to preeclampsia may develop before the onset of overt clinical manifestations of the disease. Results of ambulatory blood pressure measurements suggest that many patients who eventually develop preeclampsia may experience a decrease or disappearance of the usual decrease in blood pressure at night. Such changes usually manifest between 18 and 26 weeks of gestation. Pressor resistance appears to be altered long before systemic hypertension and proteinuria are noted. Figure 2 shows that sensitivity to the pressor effect of administered angiotensin is altered in women with a predisposition to preeclampsia. These individuals exhibit a sensitivity similar to that seen in nonpregnant women long before they clinically manifest preeclampsia. In contrast, claims that high cardiac output necessarily precedes the development of preeclampsia appear to be based on an insufficient evidence base [3].

Renin levels actually decrease in preeclamptic patients but remain significantly higher than in non-pregnant women. Similar changes are also seen in circulating levels of aldosterone and angiotensin II. Maintaining relatively high levels of these hormones may be critical because more often than not, plasma volume is relatively reduced in patients with preeclampsia.

The dramatic improvement in renal function seen in women who have had a physiologic pregnancy is offset in women who develop preeclampsia. CKF and renal blood flow decrease. The severity of the decrease is highly variable and correlates with the overall severity of the disease. If proteinuria develops, which is most common, and a renal biopsy is required, this usually shows glomerular endotheliosis. This lesion, although not restricted to pregnancy, is characteristic of women with preeclampsia. This endothelial abnormality is consistent with the notion that endothelial damage plays a key role in the pathophysiology of this systemic condition without the kidneys being affected. These hemodynamic and endothelial changes also make the kidneys more vulnerable to the development of acute renal failure (acute tubular necrosis) and, less commonly, a special form of acute, often irreversible renal failure known as renal cortical necrosis. Cortical necrosis is seen almost exclusively in severe preeclampsia and rarely occurs outside pregnancy [9].

Although preeclampsia appears to originate in the placenta, the most affected tissue is the maternal endothelium. The clinical manifestations of preeclampsia reflect widespread endothelial dysfunction with vasoconstriction and target organ ischemia. Systemic hypertension, renal, hepatic, and cerebral vascular pathology are hallmarks of severe preeclampsia. Taylor, Davidge and Roberts explore in depth the evidence that endothelial dysfunction is a focal point of the disease [13]. They note that endothelial “activation” and dysfunction are reflected in inadequate

vasoconstriction and a tendency toward a hypercoagulable state, as well as widespread microvascular thrombi, especially those seen almost universally in the placenta in preeclampsia. These investigators suggest that endothelial dysfunction may be manifested by altered synthesis and release of endothelial cell products. Among the various compounds acting on the endothelium are prostanoids and nitric oxide. Nitric oxide synthesis is increased in women who have had a physiologic pregnancy, whereas analysis of tissue and urine samples strongly suggests that nitric oxide production is impaired in women with preeclampsia. In laboratory animals, inhibition of nitric oxide synthase can cause a condition that resembles preeclampsia in many ways [12].

Similarly, a possible imbalance between vasodilating and vasoconstrictive prostaglandins seems to play a role. Synthesis of the vasodilator prostacyclin is increased in physiologic pregnancies, whereas more of the vasoconstrictor thromboxane is produced in women whose pregnancies are complicated by hypertension and proteinuria. It is unclear whether these particular compounds play a major role or are only part of the evolving pathophysiology. Nevertheless, a treatment strategy using low-dose aspirin has been developed to try to confirm the relationship between thromboxane and vasodilator prostaglandins because low-dose aspirin can selectively inhibit thromboxane synthesis. The results of studies on a large number of first-pregnant women who were not at high risk of developing preeclampsia did not support the benefit of this strategy. However, some advocates still hold the view that selective treatment of women who are at extremely high risk, for example because of pre-existing hypertension or kidney disease, may be beneficial. Over the past 30 years, significant progress has been made in understanding the role of immune mechanisms in the development of preeclampsia. It remains unexplained why first-born women are more susceptible to this condition, and why the high incidence of preeclampsia attacks (5-7%) reported in first-born women does not change in women having their first pregnancy with a second partner. This raised the suspicion that the immunologic difference between partners, embedded in the fetus, triggers an immune response in pregnant women. Redman et al. suggested that pre-eclampsia represents a continuum of immune-mediated inflammatory changes seen in normal pregnancy. Most researchers believe that endothelial damage, possibly caused by inflammation-induced cytokine release, is the main mechanism underlying the pathogenesis of preeclampsia [19].

It has also been suggested that immune adaptation to the fetus must be learned, and this adaptation may be relatively defective in the first pregnancy, resulting in a higher incidence of attacks of preeclampsia, which decreases in subsequent pregnancies, but to a lesser extent. This conditioning may be acquired as a result of previous pregnancies, abortion, and exposure to paternal sperm and seminal plasma. Maternal exposure to fetoplacental tissues varies with gestational age, and two interfaces have been described. Interface 1, which predominates in the first half of pregnancy, exists between maternal immune cells and invasive extravillous HLA-expressing trophoblasts in the decidual membrane. Interface 2, which predominates in the second half of pregnancy, involves syncytiotrophoblasts that contact maternal immune cells. Syncytiotrophoblasts are HLA-negative, and therefore paternal alloantigens are expressed only at interface 1, which is most active in the first half of pregnancy [18, 21]. It is tempting to speculate that those women who respond vigorously to these foreign antigens are more susceptible to developing the endothelial damage that precedes preeclampsia. It is indeed common for women to develop persistent antibodies to fetal HLA antigens of paternal origin. The presence of these antibodies significantly increases the incidence of graft rejection after transplantation. It should be

noted that the endothelium is the main site of attack of antibody-mediated rejection, which often develops under these conditions [26].

Conclusions: Hypertensive conditions during pregnancy, and its complications are a multisystem pathologic condition, and is one of the leading causes of maternal and perinatal morbidity and mortality. In this regard, the search for highly informative, economically acceptable diagnostic methods remains relevant. Application of which is possible in the screening mode. Widespread use of these methods will allow to start timely treatment and thus prevent the development of severe complications that threaten the life of mother and child.

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