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MECHANISMS

Hypertension in Pregnancy: Do We need a New Algorithm?

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ABSTRACT

Management of hypertension in pregnancy is a challenge, since the spectrum spreads from asymptomatic status to life-threatening complications like eclampsia. The time-tested American College of Obstetricians and Gynecologists (ACOG) classification fails to precisely prognosticate outcome of this complicated spectrum. Detection and risk stratification has undergone significant conceptual changes with the newer understanding of pathophysiology of this complex problem, mandating change in diagnostic algorithms. Introduction of biochemical high-risk markers like soluble fms-like tyrosine kinase 1 (sFlt-1):placental growth factor (PlGF) ratio has profoundly impacted risk stratification. A new four-question-based algorithm is suggested and its implications are discussed.

Keywords: Algorithm, Eclampsia, Hypertension, Preeclampsia, Pregnancy.

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INTRODUCTION

Hypertension is the most common medical condition complicating normal pregnancy.[1,2] It can present with different manifestations at different time lines in pregnancy, and can culminate in serious maternal and perinatal mortality and morbidity. A team management approach comprising obstetrician, cardiologist, and nephrologist is often called for, especially in complicated and high-risk cases, keeping in mind the challenges of choosing drugs that are safe in pregnancy and nursing. The sudden temporal transition of a relatively "benign" chronic hypertension in pregnancy to a life-threatening complication, like eclampsia, is often rapid and unpredictable, making it "the mother of all challenges."

The physiology, etiology, consequences, classification, diagnosis, and treatment of hypertension in pregnancy are complicated, vague, and often controversial; knowledge in this area is evolving constantly. The traditional algorithms have blind spots and grey areas that need to be addressed, especially in the background of Indian scenario.

This review and discussion is intended to analyze the present information, tweeze it, and suggest alternative classification and diagnostic algorithm suitable and practically useful to the clinicians at the bedside in India.

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CLASSIFICATION

The ACOG describes four major hypertensive disorders in pregnancy. This is a time-tested classification that is accepted worldwide and is used by the clinicians in India too. They are as follows:

- Chronic hypertension
- Preeclampsia (PE)
- Chronic hypertension with superimposed PE
- Gestational hypertension

CHRONIC HYPERTENSION

It is defined as blood pressure (BP) 140/90 mm Hg or higher that develops before 20 weeks of gestation. It is usually due to essential hypertension. Even though chronic hypertension in pregnancy is less ominous than PE, its prognosis becomes unfavorable if the patients develop superimposed PE.[1,3-6] Advanced maternal age and obesity are common associations of chronic hypertension in pregnancy. Epidemiological data show that 3.6 to 9.1% of pregnancies are complicated by chronic hypertension.

PREECLAMPSIA

Preeclampsia is a systemic syndrome characterized by widespread maternal endothelial dysfunction. It presents as hypertension that develops in the latter half of pregnancy (after 20 weeks of gestation) along with proteinuria (classically greater than 300 mg per day).

Preeclampsia can present in the absence of proteinuria, wherein there has to be features of any one of the following target organ damages (TODs).

- Neurological symptoms—headache, visual blurring
- Thrombocytopenia—platelet count <100,000/cumm
- Pulmonary edema
- Elevated hepatic transaminases enzymes (also called transaminitis)

Table 1: Key features of PE

Preeclampsia
Proteinuria > 300 mg/day
Cerebral symptoms, visual
Blurring
Hepatic enzyme elevation
Pulmonary edema
Renal:creatinine > 1.1 mg%
Platelet count < 100,000

- Renal insufficiency—elevated serum creatinine >1.1 mg/dL (Table 1).

ECLAMPSIA

A severe and dreaded complication of PE is eclampsia, characterized by PE plus seizures (not attributable to any other causes like metabolic or neurogenic).

The HELLP syndrome, which is an acronym for Hemolysis, Elevated Liver enzymes and Low Platelet count, has poor outcome. It complicates about 1 in 1,000 pregnancies.[3,6,7] Disseminated intravascular coagulation occurs in 20% of women with HELLP syndrome, while pulmonary edema is found in 6% cases. Up to 8% of HELLP syndrome can occur immediately after delivery. Generalized activation of coagulation, fibrin cross-linking in the small blood vessels, microangiopathic hemolytic anemia, and consumption of platelets form the basic pathophysiology of this syndrome.

GESTATIONAL HYPERTENSION

Gestational hypertension (incidence 6%) develops after 20 weeks of pregnancy and is generally not associated with PE. It is said that around 25% of those diagnosed with gestational hypertension tend to develop proteinuria and overt features of PE. This makes diagnosis of gestational hypertension, more often a retrospective one, being confirmed in the postpartum state.[3]

TRADITIONAL ALGORITHM

The traditional algorithm is based on the "timing" of detection of hypertension in pregnancy. Hypertension developing for the first time before 20 weeks is more likely to be benign, while those after 20 weeks is more likely to get complicated by proteinuria and eventually develops PE (Flow Chart 1).[6,8]

So with the present algorithm, we ask two key questions (Table 2). One the timing, two, the presence of PE.

TRADITIONAL "TWO-QUESTION" ALGORITHM

Timing of onset is sometimes vague and complicated, especially in Indian context. In the Indian social scenario,

Flow Chart 1: Traditional algorithm

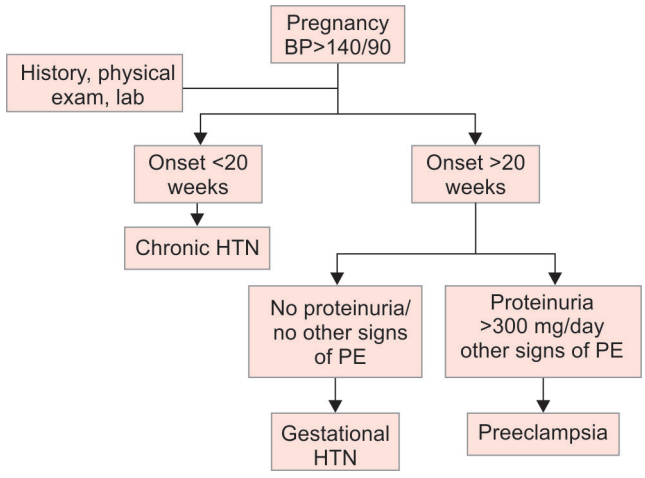


Table 2: Two key questions

Hypertensive disorders of pregnancy
Two questions • Time of onset of hypertension (<20 weeks/>20 weeks)? • Are there signs of PE/eclampsia?

the pregnant mother travels back to her parental home for confinement and that results in a change of caregiver somewhere in mid-trimester. In a poorly networked health system, it is often difficult to get hold of records of BP to risk stratify, depending on time of onset of hypertension. Similarly, many women in rural background may present late, making diagnosis on a time-scale-based algorithm problematic.

UNDERSTANDING THE PATHOPHYSIOLOGY

The systolic BP tends to remain mostly unchanged in pregnancy (slight reduction till mid-pregnancy), while the diastolic BP tends to progressively decline, reaching its lowest level between 20 and 24 weeks of gestation, presumably caused by the effects of vasodilatory neurohormones and placental arteriovenous shunts. This fall may be exaggerated in the presence of "chronic hypertension" of pregnancy. So a "slightly" high BP around 20 weeks of pregnancy might be important, and needs to be investigated to rule out early warning signs of PE. The gravid uterus in later part of pregnancy may cause compression on the splanchnic vascular beds, alter venous return, and cause change of supine BP, mandating the need for BP recording in left lateral decubitus in the pregnant mother.

Hypertension resulting from medical interaction (white coat hypertension) is estimated to be responsible for hypertension recorded during pregnancy in around 32% of cases, before 20 weeks of pregnancy. Such "spurious" high BP recording needs to be differentiated from genuine hypertension and not "overtreated" with drugs. White coat hypertension do not predispose to PE.[9]

Despite the fact that large majority of chronic hypertension are primary, young women (as compared with elderly women) are more likely to suffer from "secondary" hypertensions, like renovascular obstruction, renal parenchymal disease, adrenal pathology (aldosteronism, Cushing's syndrome, or pheochromocytoma). Ruling out such secondary pathology in pregnancy is a challenge. During normal pregnancy there is increased levels of aldosterone and renin (in contrast to increased aldosterone and decreased renin in aldosteronism), making diagnosis more difficult.

RISK TO MOTHER AND FETUS

The hypertensive mother is more likely to undergo cesarean section (in contrast to normal vaginal delivery), *abruptio placentae* leading to maternal hemorrhage, posterior reversible encephalopathy, and cerebral hemorrhage, in addition to other usual hypertensive target organ defects (retinopathy, hypertensive encephalopathy, nephropathy, and heart failure).[1,10] Control of hypertension has not conclusively shown to prevent development of such maternal complications.

Apart from higher perinatal death, intrauterine growth retardation and an increased incidence of congenital cardiac malformations are more common in pregnancy complicated by hypertension. Surprisingly, control of hypertension with antihypertensive drugs has not shown to reduce such complications.[11]

PROBLEMS OF PRESENT CLASSIFICATION

- The present classification looks at the problem from a disease purview, but from a clinical angle. A lady presenting with high BP at 20 weeks of pregnancy may be chronic hypertension (not detected during first antenatal visit or may never have had a previous antenatal visit). This is not uncommon in India, because by social diktat, the pregnant lady travels back to her parental home at a later part of pregnancy. Her antenatal records may not exist, or may not be available. This makes the present classification impractical.
- The most dreaded complication of hypertension in pregnancy is PE, but studies have shown that treating mild or even moderate hypertension does not ensure nonprogression to PE. The classification fails to prognosticate as to whether she will develop fetal or maternal complications.
- Treating the high-risk subset, on the contrary, prevents hypertensive end-organ damages. This underscores the importance of following a risk-based algorithm in deciding who would benefit from drug treatment of hypertension, rather than the type of hypertension based on a diagnosis approach (onset <20 weeks).
- It is estimated that around 30% patients presenting for the first time with high BP prior to 20 weeks of pregnancy may have white coat hypertension.[9] This underscores the need for ambulatory blood pressure monitoring (ABPM) or home BP monitoring to confirm the diagnosis.
- Once PE has been essentially ruled out, the next step is to decide the need for medical management, particularly antihypertensive drugs. Problem of the traditional algorithm of deciding and stratifying depending on the time of onset of hypertension does not help in this regard. The high-risk characters described (Table 3) indicate clear-cut need for drug therapy.[1,3,12]

A useful rule of thumb is that there is no substantial evidence that drug therapy in mild to moderate hypertension alters maternal or fetal outcome, in the absence of high-risk features as described earlier (Flow Chart 2).[13,14]

In the proposed algorithm, the diagnosis moves in steps:

Step 1. Ambulatory BP or home BP is used to confirm the presence of hypertension, since one-third of those detected to have hypertension may be "white coat effect."

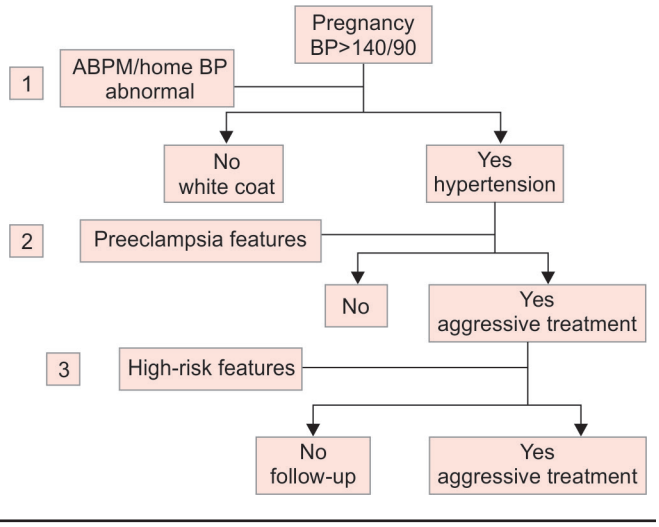
Step 2. Features of PE are checked.

Step 3. Presence of high-risk features is looked for. This identifies those who need aggressive treatment, in contrast to those who do not.

Table 3: High-risk features

High-risk hypertension in pregnancy
• BP > 160/110 mm Hg
• TOD
• Age > 40 years
• H/O stroke
• H/O eclampsia/perinatal loss
• Diabetes mellitus
• Twin pregnancy

Flow Chart 2: New algorithm



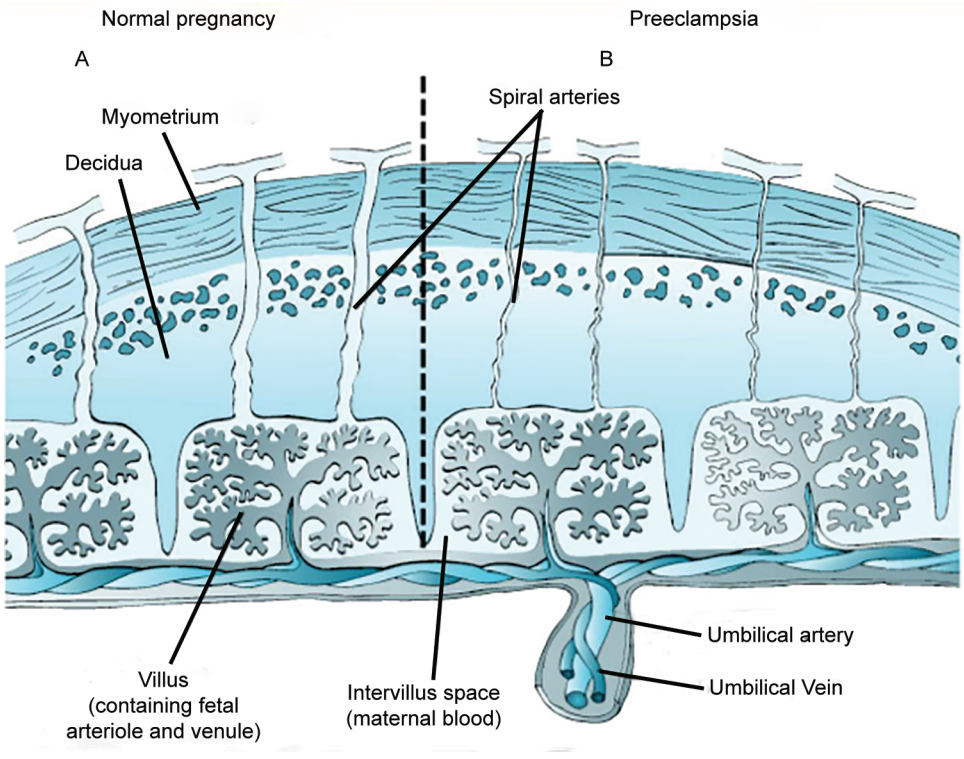


Fig. 1: Fetoplacental vasculature in normal pregnancy and PE

UNDERSTANDING PLACENTAL ABNORMALITIES

During the course of normal pregnancy, the placental cells tend to migrate up the uterine artery enabling it to remodel. This helps in hemodynamic prevention of vasoconstriction by a complex array of biochemical cascade. Abnormality of trophoblastic penetration leads to defective vasomotor function of spiral arteries, remodeling, and resultant ischemia. This results in alteration of cytokine levels, increase in endothelins, thromboxane A2, and reduction of nitric oxide and PlGF (Fig. 1).

The endothelium expresses a molecule called sFlt-1, which tend to combine with PlGF and neutralize it. During PE, the migration of the fetal cells to the uterine "spiral" artery is somehow impaired, leading to altered vasoactive neurohormones, a reduction of PlGF and increase of sFlt-1. Such biochemistry alteration remained in the area of research till recently. An elevation of sFlt-1 and reduction of PlGF have been fairly consistent and conform to the disease progression. Alteration of the ratio of sFlt:PlGF showed promise in small studies (Table 4).[15-17]

Table 4: Soluble fms tyrosine kinase 1

• sFlt-1 is a soluble receptor for vascular endothelial growth factor and PlGF
• Mainly produced by ischemic placental tissue
• Ligation of uterine arteries in primates causes elevation of sFlt-1 and syndrome of preeclampsia
• PE increases levels of sFlt-1

Table 5: Cut-off values of sFlt-1:PlGF ratio

sFlt-1:PlGF ratio
• *Gestational age >20 weeks < 38 weeks*
Ratio <38
Patient will not develop PE in 1 week
Ratio 38–85
Likely to develop PE in 4 weeks
Ratio >85
Suggestive of PE
• *Gestational age >38 weeks*
Ratio <38
Patient will not develop PE in 1 week
Ratio 38–110
Likely to develop PE in 4 weeks
Ratio >110
Suggestive of PE

A publication by Harald et al[14] clearly showed that sFlt-1:PlGF ratio in women in a developmental cohort clearly predicted development of PE. This was subsequently proved in a validation cohort in the same trial. Subsequently, development of a simple biochemical test measuring the sFlt-1:PlGF ratio changed the whole concept of preemptive diagnosis and risk prediction of hypertensive population in pregnancy.

The cut-off values are shown in Table 5.

The introduction of sFlt-1:PlGF ratio in the diagnostic algorithm makes room for a new four-question algorithm, which we feel could be simple and appropriate (Table 6).

Table 6: Four key questions

Hypertensive disorders of pregnancy
Four key questions
• Is there true hypertension?
• Are there signs of PE/eclampsia?
• Are there high-risk clinical markers?
• Is sFlt-1:PlGF ratio high?

Table 7: Termination of pregnancy on detection of PE

PE detected <34 weeks
Bed rest, BP management, close monitoring
Termination if
Maternal distress (headache, abdominal pain, HELLP syndrome)
Fetal distress
PE detected 34–37 weeks
Bed rest, BP management, close monitoring
Delivery at 37 weeks
PE detected >37 weeks
Delivery

TERMINATION OF PREGNANCY

Termination of pregnancy depends on the time at which features of PE are detected. Earlier, PE needs expectant treatment, rest, BP control. Termination of pregnancy is considered necessary in case of maternal or fetal distress.

In contrast, closer to 37 weeks, expectant management is followed by planned delivery at 37 weeks[7] (Table 7).

CONCLUSION

Managing hypertension in pregnancy is a challenge. The present algorithm based on time of onset and detection of hypertension and classifying it into gestational and chronic variety fails in the bedside because of its poor predictability of development of PE and future complications. A risk-based algorithm may be better for the clinician. Introduction of point of care biochemical risk markers (sFlt-1:PlGF) promises to bring about significant change in diagnosis and risk assessment. A new proposed simple four-question algorithm needs validation.

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