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Review Article

Hypertensive disorders in pregnancy

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ABSTRACT

Hypertensive disorders of pregnancy form the deadly triad along with hemorrhage and infection that contribute greatly to maternal morbidity and mortality rates. It complicates about 5–10% of pregnancies worldwide. Despite decades of research, it is still an enigma that how pregnancy incites or aggravates hypertension. Development of strategies to prevent and treat the disorder has been challenging due to an incomplete understanding of the pathogenesis. This article reviews the current aspect in its etiology and management of this disorder.

1. Introduction

Despite decades of intensive research, hypertensive disorders in pregnancy remain the most significant and intriguing unsolved problems in obstetrics. It is an idiopathic disorder of pregnancy characterized by development of hypertension and proteinuria developing after 20 weeks of pregnancy. It complicates about 5–10% of all pregnancies. It is the major cause of maternal and fetal morbidity worldwide, and is a leading cause of maternal and fetal morbidity and mortality.[1] Recent data estimate that, worldwide about 63,000 women die because of preeclampsia (PE) and its complications. About 98% of this mortality occurs in developing countries.[2] It is believed that the placenta play a key role in the pathogenesis, abnormal placentation occurs first, which is followed by secretion of placental toxic factors that in turn induce widespread endothelial dysfunction. This article includes a review of the disorder, their diagnosis and management.

2. Classification of hypertensive disorders in pregnancy

The working group of the National High Blood Pressure Education Program (NHBPEP) 2000,[3] has classified hypertensive disorders complicating pregnancy into the following four types:

1. Gestational hypertension
2. Preeclampsia and eclampsia syndrome
3. Preeclampsia syndrome superimposed on chronic hypertension
4. Chronic hypertension.

3. Incidence and risk factors

Preeclampsia complicates 3–5% of all pregnancies. Amongst hypertensive disorders, preeclampsia often affects young and

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nulliparous women while older women are at risk for developing preeclampsia superimposed on chronic hypertension. The factors that influence the incidence are race, ethnicity, and genetic predisposition, environmental, socioeconomic and even seasonal influences.[4] Obesity, multifetal gestation, maternal age older than 35 years, are other factors associated with preeclampsia. There is a progressive increase in the risk of PE with increasing BMI. The risk of developing PE in women with BMI <20 kg/m^2 is 4.3%, however it increases to 13.3% in women with BMI > 35 kg/m^2. Smoking during pregnancy carries an adverse outcome however, Bainbridge and associates[5] have shown reduced risk of developing hypertension in women who smoke. Ananth and colleagues[6] have shown reduced risk of hypertensive disorders in pregnancy in women with placenta previa.

The incidence of eclampsia has decreased over years due to adequate prenatal care. In developed countries its incidence probably averages 1 in 2000 deliveries but the incidence may be several times higher in the underdeveloped countries.[7.]

4. Etiology

Instead of being a simple disease, hypertensive disorders in pregnancy appears to be a culmination of factors that likely involve a number of maternal, placental and fetal factors. Following are the important factors:

1. Placental implantation with abnormal trophoblastic invasion of uterine vessels
2. Immunological maladaptive tolerance between maternal, paternal (placental) and fetal tissues
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
4. Genetic factors

4.1. *Abnormal trophoblast invasion*

In normal implantation, the uterine spiral arterioles undergo extensive remodeling as they are invaded by endovascular trophoblasts. These cells replace the vascular endothelial and muscular linings to enlarge the vessel diameter. In pregnancies destined to be complicated by preeclampsia, transformation of spiral arterioles is impaired with suboptimal remodeling of small capacitance constricted vessels into dilated large capacitance conduits.

4.2. *Immunological factors*

Loss of maternal immune tolerance to paternally derived placental and fetal antigens is another theory which has been accounted for preeclampsia syndrome. The risk of preeclampsia is appreciably enhanced in circumstances in which formation of blocking antibodies to placental antigenic sites might be impaired. Further immune dysregulation also explains an increased risk when the paternal antigenic load is increased. Redman[8] and colleagues found that early in pregnancy destined to be preeclamptic, the extra villous trophoblast express reduced amounts of immunosuppressive human leukocyte antigen G(HLA-G). This may contribute to defective placental vascularization.

4.3. *Genetic factors*

Preeclampsia is a multifactorial, polygenic disorder. Ward and Lindheimer[9] observed that the risk of preeclampsia was 20–40% for daughters of preeclamptic women; 11–37% for sisters of preeclamptic women; and 22–47% in twin studies. Nilsson and coworkers[10] reported 60% concordance in monozygotic female twin pairs. Ward and Lindheimer[9] found more than 70 genes that have been studied for their possible association with preeclampsia. The genes frequently studied are MTHFR (C677T), Factor V Leiden mutation, ACE (I/D intron 16), NOS 3(Glu 298 Asp), F2 (G20210A). But because of the heterogeneity of the preeclampsia syndrome, the complex interaction with genetic and environmental factors, it is unlikely that one candidate gene will be found responsible.

5. Pathogenesis

The pathogenesis of hypertensive disorders originates in the placenta. The prevailing theory has been that relative placental ischemia causes release of vasoactive factors into the circulation which then gives rise to endothelial-mediated end organ damage and clinical manifestations of the disease. The following are the key elements in disease pathogenesis:

5.1. *Vasospasm*

Pregnant women normally develop refractoriness to infused vasopressors[11] but those who subsequently became hypertensive lose this refractoriness several weeks before the development of the hypertension. Volhard proposed the concept of vasospasm by his direct observation of small blood vessels in the nail beds, ocular fundi, and bulbar conjunctivae. Vasospasm causes increased resistance to flow with subsequent development of hypertension.

5.2. *Endothelial cell activation*

Intact endothelium has anticoagulant properties, the cells blunt the response of vascular smooth muscle to agonists by releasing nitric oxide. Gant and coworkers[12] have shown that damaged or activated endothelial cells produce less nitric oxide and secrete substances that promote coagulation and increase vessel sensitivity to vasopressors. In the past two decades, endothelial cell activation has become the centerpiece in the understanding of the pathogenesis of PE. In this, unknown factor(s), likely placental in origin are secreted into the maternal circulation and provoke activation and dysfunction of the vascular endothelium. Glomerular capillary endothelial morphology, increased capillary permeability and elevated blood concentrations of substances associated with endothelial activation are indicative of endothelial activation.