

Hypertensive disorders in twin pregnancy

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ABSTRACT

Hypertensive disorders such as gestational hypertension, preeclampsia, eclampsia and HELLP syndrome are one of the most common pregnancy-associated entities that imply substantial maternal-fetal mortality and morbidity. When hypertensive disorders are associated with a multiple pregnancy, the onset is established sooner, with a rapid evolution and a more severe development. Although, the pathophysiology of hypertensive disorders is not fully understood, there are several risk factors that could be identified. A multiple pregnancy implies additional risks due to specific features: larger or multiple placentas, failure of the uteroplacental unit to uphold the natural development of multiple fetuses or elevated risk of abnormal placental site. Hypertensive disorders include complications that are common for both single and multiple pregnancies, complications such as kidney failure, liver dysfunction, neurological or hematological malfunction, among others. Maternal features, including mean arterial blood pressure, uterine artery pulsatility index and blood levels of PAPP-A and/or PIGF could be determined at an early age and used as screening methods.

Keywords: hypertensive disorders, twin pregnancy, preeclampsia, HELLP syndrome

BACKGROUND

Pregnancy represents an eventful experience in a woman's life, with important cardiovascular and hemodynamic alterations in order to sustain fetal and placental growth. An imbalance of the hemodynamic changes might lead to disorders such as hypertension or preeclampsia, among others. Germain and al analysed the axiom that stated that endothelial dysfunction could be a starting point for adverse outcomes during pregnancy or injurious cardiovascular events at an older age [1]. Preeclampsia is defined as the recent establishment of hypertension after 20 weeks of pregnancy, oftentimes associated with proteinuria, but not exclusively, as other risk factors might be present in the absence of proteinuria [2] as they are noted in table 1.

Per contra, gestational hypertension develops in a formerly normally blood pressure woman, after 20 weeks of gestation and implies a systolic blood pressure of minimum 140 mmHg with or without diastolic blood pressure of a minimum 90 mmHg [3], while preeclampsia develops when systolic blood pressure exceeds systolic blood pressure of 160 mmHg and diastolic blood pressure of 110 mmHg [4]. Proteinuria at the time of pregnancy is characterized by a minimum of 300 mg/dl of protein in a daily urine acquisition or a minimum proportion of protein-to-creatinine of 0.3, dipstick urinalysis accounted as an alternative method when rapid results are needed, 2+ being taken into consideration as a positive result [5]. As above-mentioned, gestational hypertension is established in a formerly normally blood pressure woman, after 20 weeks of gestation

with a systolic blood pressure of minimum 140 mmHg with or without diastolic blood pressure of a minimum 90 mmHg. As Sibai noted, proteinuria or organ deterioration might occur in up to half of the pregnant women diagnosed with gestational hypertension, especially when the diagnosis is established before the third trimester of pregnancy [6]. Accounted as a severe form of preeclampsia, implying elevated maternal mortality and morbidity, HELLP syndrome is defined by hemolysis: lactate dehydrogenase of a minimum 600 IU/l, high liver enzymes more than double of the upper limit and low platelet, beneath $100 \times 10^9/l$ and as Barton noted, it involves a well-defined management plan, sometimes, after 34 weeks of gestation, implying the need for delivery [7].

TABLE 1. Risk factors of preeclampsia [2]

First pregnancy
Multiple pregnancies
History of preeclampsia in previous pregnancies
Carbohydrate metabolism disorders
Pregestational hypertensive disorders
Autoimmune disorders
A high Quetelet index
Prothrombotic state
Nephropathy
Older parous woman
Fertility treatments
Sleep apnea

METHODS

In order to obtain a systematic literature review, medical databases such as PubMed and Google Scholar were searched, using key words such as hypertensive disorders, twin pregnancy, HELLP syndrome and preeclampsia. The search resulted in over 200 articles for analysis related to the chosen subject, from which only 23 papers were further reviewed and included in the final review.

PATHOPHYSIOLOGY

Dekker and Sibai studied the hypotheses that involved the etiology of preeclampsia: placental ischemia-increased trophoblast deportation, ischemia leading to endothelial cell dysfunction; very low-density lipoprotein versus toxicity-preventing activity in which non-esterified fatty acids are activated as a result of an elevated energetic expenditure during the pregnant months; immune maladaptation that involves

interaction between decidual leukocytes and invading cytotrophoblast in which high rates of cytokines, proteolytic enzymes and free radical species are being discharged; genetic imprinting, implying a single recessive gene or a dominant gene with incomplete penetrance [8].

Physiologically, hypervolemia is a sign of a normal pregnancy, contrasted by hemoconcentration which is associated with hypertensive disorders [9]. Vasospasm is a frequently described event during hypertensive disorders, as a result of the interaction between vasodilators such as nitric oxide and prostacyclin and vasoconstrictors such as thromboxane A2 and endothelins [10]. Using invasive hemodynamic monitoring, Hankins et al. studied eight primigravid women diagnosed with eclampsia and concluded that hemodynamic status is undoubtedly altered by disparity in fluid management, therefore a proper management should consider constraint of fluid, in order to avoid pulmonary edema [10]. Hematologic changes include thrombocytopenia as a result of platelet activation, aggregation and consumption, hemoconcentration due to vasospasm and hemolysis reflected in high LDH more than 600 IU/l discharged from erythrocytes [11]. Periportal necrosis is the leading cause of elevated liver enzymes, while LDH might result from ischemic or necrotic tissues, as well as from the destruction of erythrocytes. Hepatic changes during hypertensive disorders are also reflected by an elevation of the bilirubin level or changes in the blood coagulation parameters. A special attention is given to the renal changes that occur in a pregnant woman when hypertensive disorders are diagnosed. Endothelial cells are enlarged, containing a large quantity of fibrils, mesangial cells are expanded and proteins are deposited at the subendothelial level [12]. Tubular permeability is enhanced and it facilitates the passage of albumin, globulin, transferrin and hemoglobin, but tubular reabsorption of calcium is increased. Renal vasospasm leads to oliguria. Uric acid increases in hypertensive disorders due to a high production and reabsorption and diminished excretion in the proximal renal tubules [13].

SPECIFIC FEATURES OF TWIN PREGNANCY

A multiple pregnancy implies additional risks due to specific features: larger or multiple placentas, placental cluster or failure of the uteroplacental unit to uphold the natural development of multiple fetuses as they are listed in Table 2. Compared to a single pregnancy, a multiple pregnancy can lead to higher rates of hypertensive disorders like preeclampsia, gestational diabetes, preterm birth, intrauterine growth restriction, increases perinatal death or the

risk of operative delivery or a complicated delivery [14].

TABLE 2. Specific features of multiple pregnancies that can lead to higher complication rates

Larger placenta
Multiple placentas
Placental cluster
Failure of placental unit to uphold natural development of multiple fetuses
Substandard placental implantation
Elevated risk of abnormal placental site

According to the current literature, preeclampsia complicates 2-5% of all pregnancies and multiple pregnancies are noted to be an autonomous risk factor for hypertensive disorders, 3.50 times higher in dizygotic twins compared to monozygotic twins and 2.61 times higher in the monozygotic pregnancy [15], the risk of severe hypertension being 2-3 times higher in a multiple pregnancy [16]. Hypertensive disorders include complications that are common for both single and multiple pregnancies, complications such as kidney failure, liver dysfunction, neurological or hematological malfunction, uterine placental dysfunction or intrauterine fetal growth restriction. According to Okby et al., a retrospective population-based cohort study comparing maternal and neonatal outcome in IVF vs. spontaneously conceived twins, concluded that preeclampsia is prevailing in IVF twins compared to spontaneous twin pregnancies [17]. There are several risk factors that contribute to the higher incidence of hypertensive disorders: higher childbearing age, high BMI, diabetes, chronic hypertension, antiphospholipid syndrome, chronic kidney disease and lupus erythematosus. In a nested case-control study within the Calcium for Preeclampsia Prevention trial, which involved healthy nulliparous women, the pathogenic role that could lead to endothelial dysfunction was studied and included extreme placental anti-angiogenic factors and tyrosine kinase 1 (sflt1) that have the role to antagonize vascular growth factor (VEGF) and placental growth factor (PIGF) [18].

THE MANAGEMENT OF A MULTIPLE PREGNANCY COMPLICATED WITH A HYPERTENSIVE DISORDER

The management of a multiple pregnancy complicated with a hypertensive disorder is comparable to the management of a singleton pregnancy and includes prevention using antiplatelet drugs, notably aspirin, Duley and al. concluding that antiplatelet treatment starting at 12 or 16 weeks of pregnancy leads to a 53% lower relative risk (95% confidence interval: 35% to 66%) [19]. The antiplatelet treatment determines invasion and migration of trophoblastic cells into the uterine artery, interposing with cytokine generation and promoting the establishment of the angiogenic protein placental growth factor (PIGF), proceeding to the inhibition of apoptosis and early uterine artery remodeling [20]. Regarding the dietary supplements, preeclampsia could be determined by a rich carbohydrate regimen, the inadequacy of protein, iron and other micronutrients, so their supplementation is included in the prevention management therapy [21]. Maternal features, including mean arterial blood pressure, uterine artery pulsatility index and blood levels of PAPP-A and/or PIGF could be determined at an early age and used as screening methods [22]. According to NICE recommendations, preeclampsia, especially diagnosed after 37 weeks of gestation, implies delivery as soon as possible as a curative treatment [23].

CONCLUSIONS

There is a continuous raise in the age of women who give birth for the first time, thus this feature leading to high rates of assisted reproductive treatment usage and to a higher incidence of multiple pregnancies. Despite these well-known facts, the literature on multiple pregnancies complicated with hypertensive disorders is limited when compared to singleton pregnancies. Undoubtedly, twin pregnancies imply a higher risk factor for hypertensive disorders when compared to a singleton pregnancy. The outset is established sooner, with a rapid evolution and a more severe development. More studies are needed to be implemented in order to successfully identify the proper pathophysiology of hypertensive disorders in a twin pregnancy.

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