Hypertension and Pregnancy: an important issue

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ABSTRACT

Hypertensive disorders of pregnancy are the common medical disorders in pregnancy. It has effects both on expectant mother and foetus. The impact due to hypertensive disorders in pregnancy on maternal and neonatal mortality and morbidity is very high in India and other developing countries. The incidence of pregnancy induced hypertension in India is about 7-10% of all antenatal admission. Severe forms of hypertensive disorders of pregnancy like eclampsia is a major cause of maternal mortality. Hypertensive disorders in pregnancy complicate 1 in 10 pregnancies, often associated with maternal and neonatal mortality and morbidity. Pregnancy induced hypertension is one of the common medical disorders of pregnancy. It complicates 6 to 8% of pregnancies and is the third common cause for maternal mortality and morbidity next to haemorrhage and infections. 18% of maternal deaths are due to pregnancy related hypertension complications. It affects both mother and foetus. Hypertension during pregnancy predisposes to complications like eclampsia, abruptio placentae, disseminated intravascular coagulation, pulmonary oedema, blindness, cerebrovascular haemorrhages, HELLP syndrome, foetus growth restriction and foetal demise. Controlling hypertension in pregnancy prevents complications both in mother and foetus. There are various theories for the aetiology of pregnancy induced hypertension. The common pathophysiological changes seen are imbalance between vasoconstrictor thromboxane and vasodilator prostacyclin resulting in generalised vasospasm. This leads to endothelial damage resulting in release of vasoactive substances. This causes decreased intravascular volume and increased extravascular volume. The effects of this are placental insufficiency resulting in complications. Controlling hypertension in pregnancy using antihypertensive drugs brings down these complications. In this review, we will briefly discuss about Pregnancy induced Hypertension, its pathophysiology, diagnosis and its management.

Key words: Pregnancy induced Hypertension, Pathophysiology, management

INTRODUCTION

Hypertensive disorders of pregnancy are the common medical disorders in pregnancy. It has effects both on expectant mother and foetus [Yucesoy et al., 2005; Duley, L., 2009; Steegerset al., 2010]. The impact due to hypertensive disorders in pregnancy on maternal and neonatal mortality and morbidity is very high in India and other developing countries [Xiong et al., 2007; Moodley, J., 2011]. The incidence of pregnancy induced hypertension in India is about 7-10% of all antenatal admission [Shruti et al., 2008]. Severe forms of hypertensive disorders of pregnancy like eclampsia is a major cause of maternal mortality [Huang Y., 2001; Bell, M.J., 2010; Soares et al., 2009]. Hypertensive disorders in pregnancy complicate 1 in 10 pregnancies, often associated with maternal and neonatal mortality and morbidity [Jain, L., 1997].

Classification of hypertensive disorders in pregnancy:

There were various classifications for hypertensive disorders in pregnancy based on diagnostic criteria [WHO. 1987; Davey, D.A. and MacGillivary, I., 1998; Helewa et al.,1997; Brown et al., 2000; NHBPEP., 2000].The widely accepted classification presently is International Society for the Study of Hypertension in Pregnancy (ISSHP) [Brown et al., 2001].

According to this classification there are four categories (1) preclampsia (2) chronic hypertension –

essential or secondary (3) pre-eclampsia superimposed on chronic hypertension and (4) gestational/pregnancy induced hypertension. The term gestational hypertension was adopted by working group of NHBPEP (2000) to replace pregnancy induced hypertension [Brown et al., 1999; Leeman, L. and Fontaine, P., 2008]. Pre-eclampsia as per ISSHP classification is defined as new onset hypertension of more than 140/90 mm of Hg after 20 weeks gestation, proteinuria more than 300mg/day or a spot urine protein/creatinine ratio ≥ 30 mg protein/mmol creatinine [Brichant et al., 2010]. This definition is for the purpose of research. But when there is evidence of foetal growth restriction or end organ damage without proteinuria, the said clinical condition is branded clinically as pre-eclampsia as per ISSHP. This syndrome occurs in 5 to 8% of all pregnancy. Chronic hypertension is defined as BP > 140/90 mm of Hg before pregnancy or before 20 weeks gestation, complicates 3% of pregnancies. When there is proteinuria of more than 300 mg/day or evidence of foetal growth restriction in cases of chronic hypertension this condition is termed as pre-eclampsia superimposed on chronic hypertension. Gestational hypertension is also called as pregnancy induced hypertension. In gestational hypertension there is appearance of hypertension after 20 weeks gestation without proteinuria [Higgins et al., 2001; Medina Lomeli et al., 2005]. The hypertension subsides after delivery within 12 weeks. The term gestational hypertension or pregnancy induced hypertension (PIH) and pre-eclampsia are clinically more often considered as same with reference to management. The transition from pregnancy induced hypertension to pre-eclampsia is ill defined so both are considered as one for management. But prognosis for pregnancy induced hypertension is better than pre-eclampsia [Brown et al., 1999; Homer et al., 2008]. The incidence of pregnancy induced hypertension in India is about 7-10% of all antenatal admission [Shruti et al., 2008].

PATHOPHYSIOLOGY

Pregnancy induced hypertension is characterized by vasospasm, endothelial cell damage resulting in activation of coagulation system [Haram et al., 2000; Granger et al 2001a; Chandiramani et al., 2010].

Vasospasm

A reduction in the synthesis of vasodilator nitric oxide (NO) and an increased production of endothelin by the vascular endothelium in pregnancy induced hypertension could account not only for characteristic vasospasm but also for activation of circulating platelets. Vasoconstriction causes resistance and subsequent hypertension. Associated endothelial damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen are deposited sub endothelially with diminished blood flow because of mal distribution; ischemia of surrounding tissues would lead to necrosis, haemorrhage and other end organ disturbances characteristic of the syndrome.

Endothelial cell activation

Various noxious placental factors released by ischemic changes and toxic radicals generated by oxidative stress cause activation and dysfunction of vascular endothelium. Intact endothelium decreases responsiveness of vascular smooth muscles to agonists by release of nitric oxide and it also has anticoagulant properties. Damage or activated endothelium secretes substances that promote coagulation and increased sensitivity to vasopressors. Increased circulating fibronectin, factor VIII antigen and thrombomodulin, all markers of endothelial dysfunction are reported in pregnancy induced hypertension/preeclampsia [Granger et al 2001a].

Enhanced pressor responses

Normal pregnant women are refractory to infused vasopressors like angiotensin II. However women who are destined to develop pregnancy induced hypertension/pre eclampsia have increased vascular reactivity to angiotensin II. This increased sensitivity precedes the onset of hypertension. Autoantibodies are thought to activate AT1 receptors and increased angiotensin II sensitivity. Up regulation of bradykinin receptors (B2) leads to heterodimerisation with angiotensin II type I receptors (ATI). ATI/B2 receptors have been shown to increase responsiveness to angiotensin II in-vitro.

Prostaglandins

Endothelial prostacyclin (PGI2), a vasodilator; its production is decreased in pregnancy induced

hypertension/pre eclampsia mediated by phospholipase A2. Thromboxane A2 (vasoconstrictor and platelet aggregator) levels are increased. The prostacyclin: Thromboxane A2 ratio decreases, these changes result in vasoconstriction and hypertension. In normal pregnancy, PGI2 is more than TXA2=Vasodilation=No hypertension. In Pregnancy induced hypertension, PGI2 is less than TXA2=Vasoconstriction=hypertension [Chen et al., 1993].

Nitric oxide

Nitric oxide is a potent vasodilator, synthesized from L-arginine by endothelial cells. Nitric oxide maintains the normal low pressure vasodilated state of foeto placental circulation in humans. Pregnancy induced hypertension/preeclampsia is associated with decreased endothelial nitric oxide synthesis which increases the cell permeability.

Endothelin

Endothelin-1 is the primary isoform produced by human endothelium. These alpha 1- amino acid peptides are potent vasoconstrictors; levels in pregnancy induced hypertension/pre eclampsia are higher when compared to normotensive pregnancies in response to endothelial activation.

Circulating angiogenic factors

Vascular endothelial growth factors (VEGF) are endothelial specific growth factors plays a key role in promoting angiogenesis; placental growth factor (PLGF) is another member of VEGF family that is made predominantly in placenta. Activity of VEGF is mediated by interaction with two high affinity receptor tyrosine kinases: Kinase insert domain region (KDR) and fms like tyrosine kinase-1 (flt-1).These are expressed an endothelial surface. Alternative splicing of flt-1 results in production of sflt-1; this cannot attach to cell membranes and is secreted in to the maternal blood. It can antagonize VEGF and PLGF by binding to it and preventing its interaction with endogenous receptors. Excess sflt-1 production is seen in pregnancy induced hypertension/pre eclampsia placentas, which creates an antiangiogenic state and plays a causal role in the pathogenesis of maternal syndrome in pregnancy induced hypertension/pre eclampsia. VEGF is known to stimulate angiogenesis as well as to promote vasodilation by increasing production of nitric oxide and prostacyclin, signalling molecules that are decreased in pregnancy induced hypertension/pre eclampsia. PLGF is important in vasculogenesis and control of microvascular permeability [Wang et al., 2009].

DIAGNOSIS OF PREGNANCY INDUCED HYPERTENSION [MAGEE ET AL., 2008]

Diagnosis is based on measurement of BP and proteinuria.

Measurement of BP

1. BP should be measured with women in the sitting position with the arm at the level of the heart.
2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used.
3. Korotkoff phase V should be used to designate diastolic BP.
4. If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements.
5. BP can be measured using a mercury sphygmomanometer.

Measurement of proteinuria

1. All pregnant women should be assessed for proteinuria.
2. Urinary dipstick testing may be used for screening for proteinuria, when suspicion on preeclampsia is low.
3. More definitive testing for proteinuria (by urinary protein: creatinine ratio or 24 hour urine collection) is encouraged when there is a suspicion of preeclampsia.

Diagnosis of hypertension

1. The diagnosis of hypertension should be based on office or in- hospital BP measurements.
2. Hypertension in pregnancy should be defined as a diastolic BP of ≥ 90 mm Hg, based on the average of at least two measurements, taken using the same arm.
3. Women with a systolic BP of ≥ 140 mm Hg should be followed closely for development of diastolic hypertension.
4. Severe hypertension should be defined as a systolic BP of ≥ 160 mm Hg or diastolic BP of ≥ 110 mm Hg.

5. For non-severe hypertension, serial BP measurements should be recorded before a diagnosis of hypertension is made.
6. For severe hypertension, repeat measurements should be taken for confirmation in 15 minutes.

MANAGEMENT

Obstetric management

The only definitive treatment for the pregnancy induced hypertension is delivery. For this reason, delivery is indicated in women with pregnancy induced hypertension at term (37 weeks or more completed weeks) of any severity and in preterm with severe disease [Sarsam et al., 2008]. There are however several exceptions to these general rules [Chung et al., 2001; Weeks et al., 2005; Koopmans et al., 2007; Abdel-Hady el-S et al., 2010].

a) Less than 24 weeks

Incidence of pregnancy induced hypertension within 24 weeks is very less. In this situation with early onset pregnancy induced hypertension, continuation of pregnancy will be risky. Generally termination of pregnancy will be offered to this group [Barton et al., 2001; Brichant et al., 2010].

b) 25 to 34 weeks [Witlin et al., 2000; Briones-Garduno et al., 2003; Haddad et al., 2004]

This gestational age group is intermediate; it requires close surveillance of maternal and foetal condition. The main aim is to prolong pregnancy at least till 32-34 weeks. Foetal lung maturation occurs during this 32-34 weeks gestation. If there is deterioration in the maternal and fetal condition, termination of pregnancy is indicated. If the situation warrants delivery within 32-34 weeks gestation, maternal betamethasone administration is done to enhance fetal lung maturation.

c) More than 34 weeks [Suzuki, S., 2010; Barton et al., 2001]

Pregnancies which has crossed 34 weeks the complication of Hyaline Membrane Disease of new born is less. Pregnancy can safely be prolonged if blood pressure is well controlled and foetal parameters are within normal limits. Pregnancy prolongation till 37 completed weeks is desirable. After 37 completed weeks, irrespective of severity of pregnancy induced hypertension, termination of pregnancy is to be done [Koopmans et al., 2007; Abdel-Hady el-S et al., 2010].

Anaesthesia

An assessment of the patient must take place as early as possible in view of anaesthesia. It is recommended to perform a clotting screen as close as possible to the performing of an epidural anaesthesia. The use of aspirin, if indicated for prevention of pregnancy induced hypertension, does not as such, constitute a contraindication to performing an epidural anaesthesia if, with regards to the minimum platelet count, the recommended cut-off value for the epidural and spinal anaesthesia are 75,000/l and 50,000/l respectively. Only if all of the following conditions are met; it is recommended to quickly set up an epidural anaesthesia because this will improve the blood pressure as well as the uteroplacental haemodynamic and also anaesthesia because this will facilitate the management in case of a caesarean section. Whereas methergin is contraindicated in pregnancy induced hypertension, it is possible to use oxytocin during and after labour. Before performing a spinal anaesthesia, it is recommended to restrain the administration of crystalloids to a maximum of 1000 ml. Also the intravenous antihypertensive treatment should be reduced or interrupted until complete establishment of the anaesthetic. In case a general anaesthesia is to be performed, an assessment of the criteria for difficult intubation should be performed immediately prior to the induction. The technique employed should be a rapid sequence induction with intubation, while preventing a surge in blood pressure induced by tracheal intubation. Difficulties to extubate should systematically be anticipated. It is possible to perform a loco-regional anaesthesia following an eclamptic crisis if the following conditions are met: In case of overlapping seizures and/or impaired consciousness, a general anaesthesia is recommended [Aya et al., 2010].

Mode of delivery

Since the treatment of pregnancy induced hypertension is delivery. Deliveries before term poses risks to the new born like hyaline membrane lung disease, hypoglycaemia, hypomagnesaemia, hyperviscocity, low birth weight etc.,[Ye et al., 2010]. These problems can be averted if pregnancy is

prolonged till term provided blood pressure in under control and satisfactory maternal and foetal conditions. Induction of labour is done on reaching 37 completed weeks, uncontrolled maternal blood pressure and deterioration in maternal and foetal condition [Haddad et al., 2010]. Close monitoring of blood pressure and maternal and foetal parameters are integral part of management of pregnancy induced hypertension. Use of diuretics for preventing preeclampsia and its complications cannot be recommended [Churchill et al., 2007]. Induction of labour is done if Bishop Score of Cervix are favourable. Bishop score takes considers the following [Suzuki, S., 2010].

a) Cervical length
b) Cervical position
c) Cervical consistency
d) Cervical dilatation
e) Position of foetal head. Each parameter is given score 0, 1 and 2.

Total score more than 6-7 is considered favourable. In unfavourable cervix, pre-induction cervical ripening (to improve Bishop Score of cervix) is done using dinoprostone gel (Prostaglandin E2) intracervical application. In some cases distended Foleys catheter bulb is also used for pre cervical ripening. Induction of labour is done using intravenous escalating dose of injection oxytocin in the dose 5 to 25 mU/minute with increments every 20 to 30 minutes. The effective uterine contractions to be achieved are 3-5 contractions per 10 minute each lasting 30 to 40 seconds. Active labour (cervical dilation more than 4 centimetres) is monitored for progressive descent of foetal head and cervical dilation using WHO pictogram. If there is abnormality in the progression of labour, foetal or maternal condition deterioration, then caesarean section is indicated [Bao et al., 1990; Ye et al., 2010]. Operative vaginal delivery like outlet forceps or vacuum suction is done in second stage of labour, when there are foetal condition deterioration (foetal distress), poor maternal bearing down efforts and to cut short second stage of labour in severe pregnancy induced hypertension. Caesarean section involves three fold increased risk to the mother and foetus compared to vaginal delivery [Ye et al., 2010].

Postnatal assessment

High blood pressure at 6 weeks postnatal period is significant. Postnatal visit to a physician has to be performed to rule out underlying disorders such as chronic arterial hypertension, nephropathy, autoimmune disease or thrombophilia. This visit is also needed to provide information to the women about what occurred during pregnancy as well as to consider which would have to be done in case of a subsequent pregnancy. Long term outcome had also to be taken into account considering risks for cardiac, arterial, renal and metabolic diseases. This visit is of outmost importance after very early-onset preeclampsia, and especially if it has already occurred. The postnatal visit after pregnancy induced hypertension/preeclampsia represents a very demonstrative example of the role that the physician can afford to the obstetrician in the management of medical disorders occurring during pregnancy and needing a specific expertise as well as a long term follow-up [Pourrat, O. and Pierre, F. 2010]. Recurrence of pregnancy induced hypertension is around 1.9-24.9%. Mothers who had pregnancy induced hypertension have their daughters 3% of them developing pregnancy induced hypertension. Mothers who had eclampsia and pre eclampsia have their daughters 25% of them developing eclampsia and pre eclampsia [Palmsten et al., 2010].

Antihypertensive therapy

Antihypertensive therapy does not prevent preeclampsia or the associated adverse perinatal outcomes, but it decreases by half the incidence of development of severe hypertension among women with mild hypertension [Lowe, S.A. and Rubin, P.C., 1992; Magee et al., 2008]. Antihypertensive agents are mainly used to prevent and treat severe hypertension; to prolong pregnancy for as long as safely possible, thereby maximizing the gestational age of the infants; and to minimize foetal exposure to medications that may have adverse effects. During pregnancy the challenge is in deciding when to use antihypertensive medications and what level of BP to target. The choice of antihypertensive agents is less complex, since only a small proportion of currently available drugs have been adequately evaluated in pregnant women and many others are contraindicated [Podymow, T. and August, P., 2008]. As there are no guidelines available in India

regarding antihypertensive treatment in pregnancy, it is left to the decision of obstetrician to choose appropriate antihypertensive agent based on clinical experience. Methyldopa remains the most widely used drugs in pregnancy. Other drugs used in India are labetalol, nifedipine, hydralazine and β-blockers such as acebutolol, metoprolol, pindolol and propranolol.

CONCLUSION

Pregnancy induced hypertension is one of the common medical disorders of pregnancy. It complicates 6 to 8% of pregnancies [Podymow, T. and August, P., 2010] and is the third common cause for maternal mortality and morbidity next to haemorrhage and infections [Duley, L., 2009]. 18% of maternal deaths are due to pregnancy related hypertension complications. It affects both mother and foetus. Hypertension during pregnancy predisposes to complications like eclampsia, abruptio placentae, disseminated intravascular coagulation, pulmonary oedema, blindness, cerebrovascular haemorrhages, HELLP syndrome, foetus growth restriction and foetal demise. Controlling hypertension in pregnancy prevents complications both in mother and foetus. There are various theories for the aetiology of pregnancy induced hypertension. The common pathophysiological changes seen are imbalance between vasoconstrictor thromboxane and vasodilator prostacyclin resulting in generalised vasospasm. This leads to endothelial damage resulting in release of vasoactive substances. This causes decreased intravascular volume and increased extravascular volume. The effects of this are placental insufficiency resulting in complications [Haram et al., 2000; Granger et al 2001a; Chandiramani et al., 2010]. Controlling hypertension in pregnancy using antihypertensive drugs brings down these complications. The most extensively used antihypertensive drugs in pregnancy are β adrenoceptor antagonists, nifedipine, methyldopa and labetalol [Ghanem, F.A. and Movahed, A., 2008]. These drugs are used alone or in combinations in routine obstetric practice in our country. Each of these drugs have different mode of action. Nifedipine is vasodilator and calcium channel blocker. Methyl dopa is centrally acting antihypertensive. Labetolol is both α and β blocker. There were no clinical studies in which these drugs were compared in the same setting, when used orally with respect to their antihypertensive efficacy, side effects, maternal and neonatal outcome both in mild and severe PIH.

Conflict of interest: None

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