Effects of nifedipine on doppler indices of fetal middle cerebral artery and umbilical artery in managing hypertensive disorders of pregnancy

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Abstract
Background: Hypertensive disorders of pregnancy affects almost 6 percent of all pregnancies all over the world with recent statistical data showing an increase of incidence rates both in the developed and developing worlds. HDP affects uteroplacental and fetoplacental perfusion and may result into poor fetal conditions and increase morbidity and mortality. Calcium channel blockers (CCB) are the most commonly used antihypertensive oral medications in pregnancy due to effectiveness and less side effects.
Aim: To study how effective CCB are in improving uteroplacental perfusion and as to study whether lowering of blood pressure by CCB may have positive or negative impact to Doppler indices of fetal middle cerebral artery (MCA) as well as umbilical artery (UA) S/D which were measure by Doppler indices variables which include MCA peak systolic velocity (PS), MCA pulsatility index (PI), MCA resistance index (RI) and UA systolic to diastolic ratio (S/D).

Material and methodology: the study involved one hundred and twenty pregnant women with the gestation ages ranging from thirty-two weeks to forty weeks. Among them sixty were having hypertensive disorders of pregnancy including preeclampsia and sixty were normal pregnant women. In case groups blood pressure before and after at least one of medication were recorded, and Doppler ultrasound indices for fetal MCA and UA S/D after at least one week of medication was also recorded, follow up for calcium channel blocker dosage was recorded, delivery gestation age, mode of delivery and Apgar score, as well as neonate hospitalization was also recorded. In the control group, blood pressure, fetal MCA indices and UA S/D, delivery gestation age, mode and Apgar score were and related.

Results: We analyzed the results by using statistical package for social sciences (SPSS) version 20, in which Doppler indices between the case and control groups were compared. MCA Peak systolic speed, UA S/D ratio, MCA Pulsatile index and MCA resistance index mean values differences between the two groups were not statistically significant i.e. p-value >0.05 (p-value=0.68,0.062,0.18,0.115 respectively). However, in comparing resistance index (RI) between case group nifedipine users of 30mg dose per day with control group p-value was statistically significant (p-value=0.026, 95% CI =-011 to-0.007). In correlation with p-value<0.05,and measured by (coefficient β±SE): PS was affected by gestation age (β±SE=1.63±0.42) , S/D ratio was affected by gestation age(β±SE=-01±0.02), systolic blood pressure (β±SE=0.013±0.004) and age of women (β±SE=0.007±0.013), PI on the other hand was impacted by gravidity(β±SE=0.07±0.03) and preeclampsia(β±SE=0.2±0.07). RI showed correlation with chronic hypertension (β±SE=-0.08±0.03). on outcomes of pregnancy there was a relationship between S/D and Apgar score, an increase of S/D was associated with decrease of Apgar score, β±SE=-0.16±0.06,95% CI=-0.27 to 0.05, p-value=0.06. Apgar score≥8 in the control group was 52(86.7%) compared to 60(100%) in the control group. Apgar score 6-7 was 7(11.7%) in case group compared to 0(0%) in control group. There was one case 1(1.6%) with Apgar score<6 in cases group comparing to 0(0%) in controls.

Conclusion: Apart from having good effect in lowering blood pressure and having less teratogenic effects, oral use of nifedipine as an antihypertensive of choice in managing hypertensive disorders of pregnancy seem to improve uteroplacental perfusion in women with hypertensive disorders of pregnancy . Even with the use of CCB women with HDP had a high need for early termination of pregnancy compared to normotensive women . We also found out that low dose of nifedipine (30mg per day) in cases especially with preeclampsia was associated with a significantly high RI compared to those using high dose of nifedipine.

Key words: *hypertensive disorders of pregnancy, Doppler indices, middle cerebral artery, calcium channel blockers.*

INTRODUCTION

Hypertensive Disorders of Pregnancy (HDP) refers to a group of diseases manifested by elevation of blood pressure during the course of pregnancy. It includes those which existed before pregnancy as well as those which came after pregnancy as a complication of pregnancy itself. Averaged systolic blood pressure above 140mmHg and diastolic blood pressure more than 90mmHg is considered as hypertensive disorder. **Gestation hypertension also called**

pregnancy induced hypertension (PIH), Preeclampsia (PE), eclampsia, Chronic hypertension with superimposed pre-eclampsia and chronic hypertension.

Hypertensive disorders of pregnancy affect nearly 6% of all the pregnancy worldwide and is among the leading cause of perinatal mortality and morbidity. With data from recent studies showing decreased maternal deaths caused by hemorrhage and sepsis but with a significant increase death related to hypertensive disorders of pregnancy. In Tanzania for example a study conducted at Muhimbili national hospital showed that in a period of 10 years there were over 40000 hospital deaths of women who were at reproductive age and among them 1987 deaths were directly associated to reproduction, and within reproduction related deaths 34% of deaths were due to hypertensive disorders of pregnancy[1]. Not only deaths of women at reproductive age are related to preeclampsia but also other complications of reproduction are highly related to hypertensive disorders. Hypertensive disorders of pregnancy apart from endangering maternal life they also contribute largely to neonatal mortality and morbidity. Preeclampsia for example which among the most common hypertensive disorder, has surpassed other causes of neonatal deaths contributing to 7.5% of macerated late fetal deaths, 9% of fresh late fetal deaths and 10% of early neonatal deaths[2,3]. According to WHO in 2016 the rate of stillbirths worldwide was 18/1000 and the aim was to reduce the rate to 12/1000 in 2030. With 10 years to go still the workload is high, China for example has become the second country to succeed to lower the rate of still births but still there is a significant number of still births especially in rural areas[4]. Recent studies in china have shown much of the stillbirths cases are in rural areas and among other reason hypertensive disorders of pregnancy has been among big causes, others are exposure to chemicals and smoking among family members[5]. According to time of occurrence perinatal deaths are divided into late fetal (>28weeks) of gestation, early neonatal (≤7weeks) after delivery and late neonatal (>7 to <28 weeks) after delivery. Hypertensive disorders especially preeclampsia causes neonatal deaths mostly in the late fetal phase and some in the early neonatal phase due to intrauterine hypoxia and prematurity[6]. Hypertensive disorders of pregnancy are associated with intrauterine uterine growth restriction which in severe cases can lead to intrauterine fetal deaths or may harm growth of the newborns mentally and physically. This is due to the fact that hypertensive disorders such as preeclampsia are associated with compromised fetal oxygenation and nutrients supply[6-10].

Pathogenesis of Pre-eclampsia

Up to now the etiology of pre-eclampsia is not so clear but there are some theories which give explanation to what might be the reason behind etiology of pre-eclampsia. **Uterine spiral artery remodeling insufficiency and placenta perfusion insufficiency** during placentation, there is a transformation of the extra villous trophoblastic cell into interstitial extra villous trophoblast (iEVT)and endothelial extra villous trophoblast (enEVT). iEVT plays role in invasion of the endometrium to reach the myometrium 1/3. the enEVT on the other hand invades the spiral arteries endothelium and remodel the endothelium to replace normal smooth muscles cells hence reduce the resistance and facilitate blood flow. But in preeclampsia this mechanism fails resulting into high resistance and superficially implanted placenta. This in turn results into placental hypoperfusion.Placenta ischemia results into up regulation of production of anti-angiogenic factors such as soluble Fms-like tyrosine kinase-1(sFlt-1), placental protein 13 (PP13), placental growth factor (PLGF) and soluble endogin (sEng). all of these leads to systemic vascular endothelium reaction presented in preeclampsia.**Maternal-fetal immune-tolerance failure in** recent studies have revealed that immunotolerance in the maternal -fetal phase plays a very important role in placentation. Imbalance of Th1/Th2 regulated by regulatory T-cells with dominance of Th1 is associated with shallow placenta implantation hence preeclampsia. **Vascular endothelium injury** has been associated with preeclampsia. Vascular endothelial injury causes reduction of secretion of vasodilators such as nitrogen

monoxide and prostaglandin I, but vasoconstrictors such as endothelin and thromboxane secretion increase which causes increased peripheral resistance and hence hypertension as well as poor perfusion of vital organs. Pre-eclampsia is related to **inheritance**, with women from family members with history of preeclampsia being more likely to have preeclampsia than those from families with no history of preeclampsia.Recent researches have managed to associate some chromosomes with preeclampsia but exact genes responsible are not yet found. But genetic factors are so much related to environmental effect.Preeclamptic women have been found to have **deficiency of nutrients**. Mostly is deficiency of calcium, zinc, magnesium and also low plasma albumin. But still no significant research data to show as to how these deficiencies may play role in preeclampsia pathogenesis.

Pathophysiology of pre-eclampsia

In Brain pre-eclampsia causes cerebral vasospasm, increased vessel permeability resulting into cerebral edema, hematoma, regional ischemia, thrombosis as well as hemorrhage. All of them lead into CNS manifestations such as irritability, headache, coma, visual disturbance and seizures. Cerebral perfusion pressure and vessels resistance all increase the risk of herniation of the brain. CT scan is a standard way of diagnosing brain changes.**In the Kidneys** dilatation of the glomerulus results into plasma protein leakage hence protein in urine. Reduced kidney perfusion results into reduction of urine volume, both blood uric acid and creatine level increases. Further progress leads to kidney failure.**In Cardiovascular system** Vasospasm, elevated peripheral resistance, high blood pressure, injury to the cardiac muscles, increased afterload and decreased cardiac output make the CVS belong to a low output and high resistance status. Increased permeability of the vessels of the heart results into intravascular fluid infiltration into the extravascular intra myocardial space resulting into ischemia of the myocardia, interstitial edema, focal hemorrhage, pulmonary edema and then heart failure. **Hematological effects,** due to systemic vasoconstriction and increased blood vessels permeability blood concentration increases and hematocrit also increases. But with persistent elevated blood pressure blood cells destruction increases anemia and thrombocytopenia are also common. **In Uteroplacental perfusion** poor spiral arteries remodeling causes spiral artery remodeling insufficiency which is reflected by decreased diameter of spiral arteries by almost 50% as compared to normal pregnancy. Furthermore, vascular injury and placental arteries sclerosis worsens the perfusion causing fetal growth restriction, fetal distress and in some cases intra uterine fetal death.This forms the basis of my study, as mentioned above uteroplacental perfusion is markedly affected in preeclampsia, as to how much antihypertensive improve uteroplacental perfusion and fetal circulation this is the question that we expect research data will answer.**In Endocrine system** Increase of angiotensin converting hormone, in late weeks of pregnancy results into increase of mineral corticoids, and desoxycortone. Mineral corticoids play role in electrolytes balancing and determination of osmotic pressure of the plasma.

On the other hand, desoxycortone acts on the proximal tubule of the nephron to retain sodium and chloride ions by facilitating reabsorption at the same time it helps the release of potassium and hydrogen ions. So, increase of these hormones in preeclampsia is associated by sodium retention and decrease in plasma osmotic pressure. Loss of potassium result into decreased cellular osmotic pressure and retention of potassium results into increased extracellular osmotic pressure so the net results is loss of fluid from the cells and accumulation of fluid in extracellular spaces characterized by edema. But severity of edema plays no significant role in prognosis of preeclampsia. However, eclampsia can lead to worsening of metabolic imbalance due to lactic acid acidosis and respiratory acidosis.**In the liver** liver injury can be determined by checking the level of serum liver enzymes, the high the level of serum liver enzymes the severe the injury is. Liver injury is determined by portal vein surroundings hemorrhage and in severe cases there can be necrosis of tissues, hematoma of the liver membranes and finally

rupture of the liver and loss of life of both mother and fetus[11]. **Risk of fetal demise/stillbirth** the risk is high for almost 90% in the first 20 weeks of gestation and goes to 3/1000 live birth after 28 weeks of gestation. Studies shows increases in chances of still birth after 36 weeks in women with gestational hypertensive disorders. Severe preeclampsia risk or still birth goes to 21/1000 live births but normally preeclampsia accounts for 9/1000 live births fetal demise[3]. **Intrauterine fetal growth restriction (IUFGR)** as a marker of fetal well-being, HDP affects the fetal growth due to impaired blood supply secondary to placental pathological changes of HDP e.g. in preeclamsia[3,12–14]. **Hematological changes** fetal thrombocytopenia is more common in preeclampsia diagnosed in the first 2-3 days of life but resolves by day 10 of life, neutropenia is also common which is due to reduced circulating colony forming unit granulocyte macrophage (CFU-GM). **Broncho-pulmonary dysplasia (BPD)** which is a result of failure of fetal angiogenesis due to ischemia. **Neurodevelopmental** outcomes of neonates born from women with preeclampsia are surprisingly to be good and some studies have showed high scores in premature neonates of preeclamptic women than non-preeclamptic[3,15,16].

In normal pregnancy doppler indices for MCA PI and RI shows parabolic curve in the course of pregnancy with the plateau at 28-30 weeks of gestation[17]. On the other hand, UA RI and PI show gradual fall over gestation age with negative correlation. MCA PI and UA PI both show strong correlation with their RI value[17]. Abnormal wave forms of uterine and umbilical artery play important role in predicting adverse outcomes of pregnancy such as FGR and need for operative intervention during delivery and labor. This shows the need of doppler assessment in management of preeclampsia[12,18,19]. In other words that is to say sensitivity of uterine artery and umbilical artery in prediction of outcomes of pregnancy is high in HDP.Small for gestation (SGA) is more associated with decreased MCA PI values than changes in UA PI. It also showed that sensitivity, specificity and prediction values of MCA PI are better than those of UA PI in SGA. This might be useful in HDP also keeping in mind that HDP in many cases are associated with FGR. In the third trimester uterine artery flow velocity, PI and RI are good predictors of neonatal complications[20]. With many cases of HDP such as preeclampsia being more common in the third trimester, so this was also a significant note in our study. In severe hypoxia the fetal blood floor shifts to supply the brain which can be studied in the ultrasound by comparing the blood flow velocity of the umbilical artery and that of the cerebral artery. Brain sparing is a mechanism to protect the brain and to ensure normal growth of the brain and it is not an indication of the degree of brain damage[21]. There are many medications that can be used to lower blood pressure but in hypertensive disorders of pregnancy a choice of medications to be used must weighed on the outcomes of lowering blood pressure and less side effects to the fetus. Calcium channel blockers being more preferred kind of antihypertensives.

Pharmacology of CCB (nifedipine)

Management of hypertensive disorders of pregnancy have some specific target depending on severity of the disease. All the intervention measures intend to minimize the chances of the disease to progress with safety of the mother and the fetus being the first priority. So, any intervention intends to stabilize blood pressure of the pregnant woman and avoid any chance of worsening of the situation[22]. For pregnancy induced hypertension the aim is to avoid the progress to preeclampsia and for preeclampsia the aim is to avoid the chances of progressing to eclampsia[2]. All of the above-mentioned measurements also should involve fetal monitoring as well. The condition of the fetus should be monitored by electronic ways (NST) also ultrasound imaging to ensure biophysical profile of the fetus is within normal range.

Calcium channel blockers (CCB) is a group of antihypertensive which has been selected to be used as the first line oral medication used in management of hypertensive disorders of

pregnancy[8,23,24].This is highly due to the fact that CCBs are relatively safe with very good effect on lowering blood pressure[23]. Calcium channel blockers are known to have less teratogenic effects and studies have proved safety of calcium channel blockers in pregnancy[24]. But some studies showed the use of calcium may be associated with preterm delivery and low birth weight [23], but this may be due to the use of calcium is always associated with preeclampsia and threatened preterm delivery which may also cause low birth weight[25]. The most common being nifedipine which is also used in low dose to treat threatened preterm deliveries and threatened abortions due to its tocolytic effect[26]. When used for tocolysis nifedipine has showed not only relaxation of the myometrium but **dilatation of uterine artery and blood vessels of the placenta with a significant increase in the size of the placenta**[27]. This effect of dilating blood vessels of the uteroplacental phase may have effects of **fetal hemodynamics** and can be studied by **doppler ultrasound** of the umbilical artery and that of the middle cerebral artery. Calcium channel blockers are chemical substances that inhibit influx of calcium ions into excitable cells and by so doing they interfere the role of calcium as an intracellular messenger so affecting contraction of smooth muscles of the coronary circulation peripheral arteries and the myometrium[27]. The net effect is the dilatation of those smooth muscles which helps to lower blood pressure.Due to its muscle relaxation effect on smooth muscles CCBs have negative inotropic effect on the myocardia of the atria and ventricles. This makes CCBs useful in management of myocardial related complications such as angina pectoris. Is also useful in protection of damaging the myocardia in situations involving congested heart failure.

On the other hand, CCBs also affects the conduction system of the heart by inhibiting impulse formation on cells which depend on calcium for depolarization in the sinoatrial and atrioventricular nodes. CCB slows sinus pacemaker and inhibit atrial ventricular conduction.

The pharmacological effect of CCB is due to the ability to bond to L-type voltage dependent calcium channels which are located on the cells of smooth muscles of systemic arteries, coronary arteries and of the myocardia. By inhibiting these calcium channels, the net effect is decreased myoactivity of myocardia, dilatation of peripheral arteries which lowers peripheral resistance and blood pressure and coronary arteries dilatation which increases cardiac perfusion and hence protect myocardial infarction. Arterial dilatation action of the CCB can affect uteroplacental perfusion which can be measured by S/D and can have a reflection on the fetal perfusion reflected by the MCA[27–29].

Classes of CCB
1.dihydropyradines e.g. nifedipine, amlodipine etc.
2.benzothiazepines e.g. diltiazem.
3.phenylalkylamines e.g. verapamil.

Among them the mostly used in obstetrics are dihydropyridines due to their good effect in lowering peripheral resistance by acting on systemic arterial smooth muscles[24]. Also, their action is fast compared to others whose action are located in the coronary vessels and myocardia. Nifedipine is administered orally and the absorption is good, excretion is by the

kidney. The onset of action is really fast compared to amlodipine, but half life is short except for controlled release formulations which are commonly used in obstetrics.

Among other side effects the most common side effect of nifedipine is reflex tachycardia and angina worsening for patient who previously had angina. Also, some gastrointestinal manifestations such as constipation. Caution should be taken when combined with beta blockers due to a possibility of cardio depressant action. Apart from those few side effects of dihydropiridines they are still safe in pregnancy and they have been associated with good outcomes of prolonging gestation in threatened abortion and in hypertensive disorders of pregnancy[30].

Aim

Aim of our study was to find out how use of nifedipine a calcium channel blocker commonly used in treatment of hypertensive disorders of pregnancy may impact fetal hemodynamics by studying doppler indices of umbilical artery and middle cerebral artery and try to establish other factors which can affect doppler indices values.

Research methods and materials

Principles and theories

Hypertensive disorders of pregnancy affect uteroplacental and fetoplacental perfusion and hemodynamics through improper placentation i.e. shallow invasion of the placenta in the myometrium and through vascular endothelium injury which affects the placenta blood vessels which then affects growth and survival of the fetus[8,9,31].Calcium channel blockers (CCB) act on smooth muscles to dilate blood vessels and lower resistance which can have impact on uteroplacental perfusion measured by S/D and hence on the fetal hemodynamics which can be measured by MCA doppler indices[26–28]. Any pathology that results into fetal hypoperfusion results into the change of the hemodynamics of the fetus to ensure perfusion of the vital organs such as the brain, heart, kidney and the mesentery. A good example is Fetal brain sparing effect[21,32]. The middle cerebral artery doppler indices are good indicators of the fetal perfusion and can be used to reflect fetal hemodynamics in anemia and other conditions[22,33,34].Normally fetal MCA has a high resistance flow but under pathological conditions it turns into a low resistance flow to maximize perfusion of the brain.In persistent pathological conditions such as brain edema the fetal MCA reverts to high resistance flow before the pathological condition is resolved which is then associated with adverse outcomes[12,13,20,35].Under normal conditions fetal MCA PI is higher than the UA PI, MCA S/D is also higher than UA S/D, cerebral placental ratio of above 1:1 is normal and less than that is regarded as abnormal.MCA PI curve in the course of pregnancy is parabolic in shape with the peak values at 28-30 weeks of gestation[17].

Study population

The study involved a total of 120 pregnant women which were distributed equally in two groups control 60(50%) and HDP group 60(50%). All were recruited from Wuhan Union Hospital inpatient department of obstetrics and others from the outpatient clinic of the department of obstetrics between January 2019 and November 2019.

Research proposal was approved by the department in November 2018 and patients involved accepted to take part verbally.

Exclusion and inclusion criteria

No age limit was set to participants, but high-risk pregnancy was an exclusion criterion. Participant in both groups were at the gestation age of 32-40 weeks basing on LNMP and in some cases calculations were done by relying on the size of gestation sac shown on the first ultrasound report. Participant were not in labor at the time of Doppler ultrasound. Pregnancy with fetal co-morbidities associated with structural abnormalities were excluded All women had no history of smoking or taking alcohol. DM and autoimmune diseases were also ruled out to all participants. Hypertension diagnosis was according to hospital standards and guidelines.

Blood pressure evaluation

Blood pressure was measured by mercury column sphygmomanometer with the standard calf length at least 1.5 times longer than the circumference of the mid upper arm. For suspected abnormal blood pressure measurements were repeated at least two times with an interval of not less than four hours between the two measurements. Systolic blood pressure of equal and above 140 mmHg and diastolic blood pressure of equal and above 90 mmHg being taken as high blood pressure. In the HDP group blood pressure before start of medication and after stable blood pressure was attained were all recorded.

Treatment with nifedipine.

HDP group patients were all receiving oral CCB in different dosages and frequency. Commonly used CCB was nifedipine controlled release tablets (30mg) taken once, twice and thrice in some cases. In some cases, patients were taking 30mg once a day, in some cases patients were taking 30mg twice a day and in some cases, patients were taking 60mg in the morning and 30 mg in the evening. In our study we preferred patients taking nifedipine controlled release than any other medication to maintain uniformity. Blood pressure before and after was recorded. Colored Doppler ultrasound was also recorded after stabilization in all cases of HDP.Patients who were on more than one antihypertensive (CCB and any other antihypertensive) were not included as this study aimed only on the effects of CCBs particularly nifedipine.

Doppler ultrasound

Doppler ultrasound for both groups was conducted under standard conditions of room temperature at normal room temperature. Positioning was semi-recumbent position (45 degrees inclination angle). To avoid descending aorta and inferior venacava compression the patients were slightly tilted laterally. Doppler indices were recorded when the fetuses were in a resting position. Indices recorded were Umbilical artery Systolic to Diastolic ratio (S/D), Middle Cerebral Artery (MCA) Peak Systolic Velocity (PS), MCA Pulsatile Index (PI) and MCA Resistance Index (RI).

Statistical analysis

Statistical analysis was done by using IBM statistical package for social sciences (SPSS Version. 20). Continuous and categoric data were presented as mean ± S.D and percentage respectively. Comparison between groups was done by using ANOVA test for independent measures and Pearson's chi-squared test (χ^2) methods. P<0.05 was set to be statistically significant.

Results

Demographic and clinical characteristics of study patients.

The study involved 120 pregnant women at the gestation age between 32-40 weeks who were divided into case group and control group each having 60 pregnant women. Case group were hypertensive disorder of pregnancy patients using nifedipine. 10(16.7%) were diagnosed to have PIH, 31(51.7%) were diagnosed to have preeclampsia and 19(31.6) were having chronic hypertension. Mean age for the case group was 31.5±4.0 years, and for control group was 31.4±4.4 years with p-value=0.9 which was not statistically significant, mean gravidity in case and control groups was 2.12±1.0 and 2.08±0.8 respectively p-value=0.85. mean baseline systolic blood pressure for case and control groups was 144.8±9.3mmHg and 118±7.6mmHg respectively with p-value<0.0001 which was statistically significant. Mean delivery gestation age in weeks for case and control groups was 36.47±2.45 and 38.32±0.8 respectively with p-value<0.0001 which was statistically significant. In case group 5(8.3%) patients delivered by spontaneous vaginal delivery while in control group 26(43.3) delivered by SVD with p-value <0.0001. Emergency caesarean sections in case group were 23(38.3%) compared to 2(3.3%) in control group, p-value<0. 0001.On the other side the number of elective caesarean sections between the two groups was almost the same and not statistically significant. Outcomes of pregnancy with Apgar score >8 between the two groups was also statistically significant with p-value=0.006, 52(86.7%) in cases and 60(100%) in controls. See table **1.**

Doppler indices in case and control groups.

We compared the mean values of Middle Cerebral Artery(MCA) peak systolic velocity (PS), pulsatile index (PI), resistance Index (RI) and umbilical artery (UA) systolic to diastolic ratio (S/D) Doppler indices of the case group (pregnant women with hypertensive disorders of pregnancy using nifedipine) with the Doppler indices of normotensive pregnant women. Mean PS value for case group was 47.6±10.0cm/s and that of control group was 48.4±11.3cm/s, p-value=0.68 which was not significant as shown in **figure 1**.

Mean S/D ratio of case group and that of control group was 2.61±0.8 and 2.4±0.35 respectively, p-value=0.062 which was not significant. See **figure 2.**

Mean PI for the case group was 1.61±0.37, control group was 1.53±0.27, p-value=0.18 which was also not significant as shown in **figure 3**. Mean resistance index RI of case and control groups were 0.78±0.14 and 0.75±0.07 respectively, p-value=0.115 which also was not statistically significant shown in **figure 4.**

Effects of different oral Nifedipine dosages on Doppler indices

We compared the values of Doppler indices of cases using different nifedipine dosages to the values of doppler indices of the control group pregnant women(n=60). Starting with PSV, in cases using nifedipine dose of 30mg once daily(n=31), mean peak systolic speed was 50.48±11.3cm/s, 95% confidence interval (CI) =-7.1 to 2.9, p-value=0.405 which was not statistically significant. Cases using nifedipine dose of 60mg per day in (n=24) to controls(n=60), PSV was 45.17±6.99, 95% CI=-1.7 to 8.1, p-value=0.198 which was not statistically significant. Case patients using nifedipine dose of 90mg per day (n=5) compared to control (n=60), mean PS in case group was 41.05±6.0cm/s, 95% CI= -2.91 to 17.6, p-value=0.158 which was not statistically significant. See **figure 5.**

Systolic to diastolic ratio in cases using 30 mg (n=31), dose per day compared to controls was 2.48±0.4, 95%CI=-0.28 to 0.1, p-value =0.377 which was also not statistically significant. In cases using 60mg per day (n=24), SD ratio was 2.5±0.5, 95% CI=-0.32 to 0.05, p-value=0.157 which was not statistically significant. For cases using dose of 90mg per day (n=5) mean S/D ratio was 3.8±2.0, 95% CI=-2.02 to 0.86, p-value=0.284 not significant. See **figure 6.**

Mean Pulsatile index (PI) in cases using 30 mg was 1.5±0.3, 95%CI=-0.24 to 0.33, p-value=0.139 not statistically significant. In cases using 60mg mean PI was 1.6±0.4, 95% CI=-0.21 to 0.09, p-value was 0.431, also not statistically significant. In cases using 90mg per day mean PI was 1.55±0.22, 95% CI =-0.27 to 0.23, p-value =0.884 which was not statistically significant. See **figure 7.**

Resistance Index (RI) in cases using 30mg per day was 0.8±0.2, 95%CI=-0.11 to -0.007 with p-value=0.026 which was statistically significant. For cases using 60 mg per day mean RI was 0.75±0.07, 95% CI=-0.035 to 0.03, p-value=0.901 which was not statistically significant. For cases using 90mg per day (n=5), mean RI in cases was 0.75±0.04, 95% CI= -0.066 to 0.06, p-value=0.929 which was also not significant as shown in **figure 8**. The only significant difference was found in the comparison of the Resistance index RI of case pregnant women group using 30mg oral nifedipine once per day when compared to control group women in which p-value=0.026.

Predictors of peak systolic speed (PS).

A number of variables were analyzed to determine as to how much they could have impacted peak systolic speed as summarized in table 2. In univariate analysis (p<0.05), In both univariate and multivariate mode PS were correlated with gestation age, in univariate analysis β±SE=1.63±0.4, 95% CI=0.79 to 2.5 while in multivariate analysis it was 1.63±0.42, 95%CI=0.79 to 2.46, both with p-value<0.0001. See **table 2.**

Predictors of systolic to diastolic ratio(S/D)

We also analyzed S/D ration as another Doppler index of umbilical artery which is an important indicator of placenta function, S/D ratio was correlated to a number of predictors and we found out that it has linear relationship with multiple factors. In univariate analysis S/D showed correlation with gestation age β-coefficient=-0.1±0.02, p-value<0.0001, 95% CI=-0.14 to -0.04. systolic blood pressure (SBP) (mmHg) β-coefficient =0.02±0.004, p-value<0.0001, 95% CI=0.01 to 0.03. Diastolic pressure had the same β-coefficient as for SBP With SBP β-

coefficient=0.013±0.004, 95% CI=0.0006 to 0.02, p-value=0.001 which was statistically significant. Gestation age impacted S/D β-coefficient=-0.1±0.02, 95% CI=-0.11 to -0.02, p-value=0.005. On the other hand, S/D had an impact on Apgar score by 0.16, p-value=0.006. As shown in **table 3**.

Predictors of pulsatile index (PI)
Pulsatile index on multivariate analysis showed correlation with preeclampsia β-coefficient=0.2±0.07, 95% CI=0.07 to 0.33, p-value=0.004 which means preeclampsia patients has a chance of increasing pulsatile index by 0.2 times than patients without preeclampsia or normal pregnant women. There was also correlation between PI and gravidity β-coefficient=0.07±0.038, 95% CI=0.01 to 0.13, p-value=0.02 as shown in **table 4**.

Predictors of resistance index (RI)
In multivariate correlation RI showed to be affected chronic hypertension and nifedipine dosage of 30mg daily. In the effect of chronic hypertension to resistance index β-coefficient=-0.008±0.03, 95% CI=-0.13 to 0.02,p-value=0.008. Nifedipine dose of 30mg was another predictor of resistance index which have also been discussed before but in multivariate correlation the effect was in such a way that for a patient with HDP taking 30mg dose of nifedipine per day may make a chance of having elevated RI increase by 0.08 compared to those taking dose of 60mg and 90mg daily. See **table 5.**

Discussion
In demographic and clinical characteristics of the two groups there were some significant differences in some of these characteristics. There was a significant difference in the mean delivery gestation age between the two groups. The case group had the mean delivery GA of 36.47± 1.9 weeks while in the control group the mean delivery GA was 38.32±0.8 weeks, p<0.001. The reason behind the difference is for pregnant women with preeclampsia the safe delivery GA is between 34 to 36 weeks to avoid the risk of fetal demise[7]. Also mostly HDP (PE) results into preterm delivery due to the fact that fetuses are in a high risk of developing hypoxia[5,22,35,36]. So, despite of using nifedipine as an effective medication to control blood pressure and improve fetal status still preterm delivery is associated with hypertensive disorders of pregnancy. There was also a significant number of emergency caesarean sections in the case group as compared to control group, 23(38.2%) in cases and 2(3.3%) in control group, p<0.0001. The reason was HDP is not a static condition and can change any time, with close monitoring by NST, doppler USS and by assessing BPP. Significant abnormal doppler waveform of UA and MCA is always associated with poor outcomes of pregnancy[3,9,14,20]. So abnormal UA and MCA waveforms was among the criteria for emergency CS in the case group. There was also a significant difference in neonates with low score between the two groups, p<0.001. this is due to the fact that abnormal waveform of the UA and MCA doppler is always associated with poor outcomes of pregnancy due to possible severe intrauterine hypoxia which harms the fetus[21,34,36].
The cumulative effect of nifedipine on doppler indices of the UA and MCA showed no significant difference between all the doppler indices between the two groups, p>0.05. This could be due to the finding in previously done studies showing that use of nifedipine helps to dilate blood vessels of the uterus (uterine artery), blood vessels of the placenta and also causes

the increase of the placenta size which favors the uteroplacental perfusion and improve fetoplacental hemodynamics[27]. On the effects of individual doses of nifedipine on doppler indices it was found that the daily dosage of 60mg and 90mg was associated with insignificant differences of mean value of indices between cases and controls. On the other hand, patients taking 30mg of nifedipine daily had a significant mean MCA RI values between cases and controls, p<0.026. This matches with the previous studies which reported that in low dose of nifedipine used in tocolysis nifedipine helps to reduce uterine contractions but does change doppler indices and blood pressure of pregnant women[27,29]. It also shows that RI is a sensitive indicator of fetal hemodynamics status.[9,20,22,37]. In correlation with other factors it was noticed that RI correlated inversely with chronic hypertension, β=-0.08, 95%CI= -0.13 to 0.02, p=0.008, which means that chronic hypertension cases in our study was associated with decrease of resistance index. This is due to the fact that women with CHTN were on medication for a considerably long time. So, the use of antihypertensives in chronic hypertension resulted into low MCA RI value. In literature previous studies proved that among hypertensive pregnant women, women with lower blood pressure have chances of good outcomes of pregnancy[6]. So could be women with chronic hypertension had low blood pressure than those with PE, PIH etc. Pulsatility index PI had correlation with preeclampsia and gravidity, that is to say PE had the chances of abnormal RI and gravidity also can impact RI. PE correlated to RI by β=0.2, 95%CI=0.06 to 0.32, p=0.004. which was also the finding of other studies done previously, showing that abnormal waveforms of MCA PI is associated with poor outcomes, and need for emergency CS[20,22,33]. There was also a slight correlation between gravidity and PI, the higher the number of gravidities the higher the chances of getting abnormal PI waveform. SD ratio was correlated with age, β=0.007,95%CI=0.019 to 0.033, p=0.046, showing that increase in age of a pregnant woman could have the impact on the SD ratio value. Also, there was a negative correlation with gestation age, β=-0.1, 95%CI=-0.11 to -0.02, p=0.005, showing that SD ratio decreases with GA. This was shown on a study of doppler indices trending from 18 to 40 weeks which showed a down trend of SD ratio after 28 weeks[17]. Since our study involved women from 32 weeks GA so an inverse proportionality is true. There was an inverse relationship between SD ratio and Apgar score, the higher the SD value the lower the Apgar score, β=-0.016, 95%CI=0.27 to -0.05, p=0.006. this has a prediction value SD ratio can be used to predict outcomes of pregnancy, also can indicate complications of pregnancy like IUFGR and placenta dysfunctions[18,22,38,39]. Systolic blood pressure also showed correlation with SD ratio, an increase in systolic blood pressure correlated with SD ratio by β=0.13, 95%CI=0.006 to 0.02, p= 0.001, this could be the reason also for the ability to use SD ratio to predict HDP, and complications associated to HDP like placenta dysfunction[12,13,19].

Conclusion

The findings in this study shows that there was a very big similarity of doppler indices of pregnant women who were having hypertensive disorders of pregnancy who were using CCB (nifedipine) and normotensive pregnant women who were not on using nifedipine. Already previous researches have proved hypertensive disorders of pregnancy to have changes in the Doppler values of UA and MCA significantly and some studies went even further to establish prediction of outcomes of pregnancy by using Doppler indices, so this similarity in our study means that the use of nifedipine results into improvement of uteroplacental and fetoplacental hemodynamics. Apart from improving doppler indices among pregnant women with hypertensive disorders of pregnancy but still hypertensive disorders of pregnancy were associated with a significant number of preterm deliveries as compared to normotensive pregnant women. As a precaution to prematurity prevention all neonates delivered before term were sent to neonatal unit for observation which was a useful clinical practice to reduce the risk of unnoticed early neonatal complications. We found out that resistance

index (RI) to be a sensitive indicator of the effects of nifedipine on Doppler indices as it was able to show some significant difference between nifedipine users pregnant women and normal pregnant women. Not only that but when related to diagnosis, it was found that RI was lower in pregnant women with chronic hypertension and were on regular medication before they became pregnant and they continued to use antihypertensive in the course of their pregnancy than in pregnant women with PIH and PE. Furthermore, our study found out that systolic to diastolic flow ratio (S/D) after 32 weeks of gestation was a good predictor of outcomes of pregnancy than other Doppler indices, higher S/D values were associated with low Apgar score. This could be more evident if the sample size of my study could have been larger, so more studies involving larger samples and more close monitoring of adherence to CCB which may include more factors than those used in our study may help to get more detailed facts on the impacts of CCB on Doppler indices in the future.

Availability of data
Data and materials collected in the course of this study can be available by reasonable request to the corresponding author.

Authors' contributions
KHA and WM collected patients history and physical examination, ZJW and WM planned treatment plans, ZJW, WM and KHA did interpretation, KHA and SSS collected and organized results, MMM and KHA did statistical analysis, KHA wrote the preliminary manuscript, MMM, SSS, WM and ZJW participated in manuscript review and editing. All authors read and approved the manuscript.

Ethics approval and consent to participate
Ethical clearance was sought from Tongji Medical College Ethical committee of Huazhong University of Science and Technology (proposal was presented to the Ethical committee on November 6,2018) after review by the committee permission was granted to conduct the study. No any written document was given.

Competing interests
The authors declare that they have no conflict of interest.

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Attachment 1
List of tables

Table 1

Demographic and clinical characteristics of study patients

Variable	Nifedipine group (n = 60)	Control group (n = 60)	P-value
Age (yrs)	31.5±4.0	31.4±4.4	0.9
Gravidity (No)	2.12±1.0	2.08±0.8	0.85
Gestation age (weeks)	32.2±2.45	34.25±1.9	0.59
Systolic blood pressure (mmHg)	144.8±9.3	118.4±7.6	<0.0001
Diastolic blood pressure (mmHg)	98.6±6.3	74.17±6.05	<0.0001
Delivery gestation age (weeks)	36.47±1.9	38.32±0.8	<0.0001
Spontaneous vaginal deliverly, No (%)	5(8.3)	26(43.3)	<0.0001
Elective caeserean section, No (%)	32(53.3)	32(53.3)	1
Emergency caeserean section, No (%)	23(38.3)	2(3.3)	<0.0001
Apgar score ≥ 8, No (%)	52(86.7)	60(100)	0.006

Apgar score 6 to 7, No (%)			7(11.7)	0(0)	0.013	
Apgar score < 6, No (%)			1(1.7)	0(0)	1	
Pregnancy induced hypertension, No (%)			10(16.7)	0(0)	0.001	
Preeclampsia, No (%)			31(51.7)	0(0)	<0.0001	
Chronic hypertension, No (%)			19(31.7)	0(0)	<0.0001	
Nifedipine daily dose, 30mg, No (%)			31(51.7)	0(0)	<0.0001	
Nifedipine daily dose, 60mg, No (%)			24(40)	0(0)	<0.0001	
Nifedipine daily dose, 90mg, No (%)			5(8.3)	0(0)	0.057	

Data are expressed in mean±standard deviation unless otherwise stated

Table 2

Univariate and multivariate linear regression model for determining predictors of peak speed.

	Univariate analysis			Multivariate analysis		
Variable	Coefficient β±SE	P-value	95% CI	Coefficient β±SE	P-value	95% CI
Gastation age (wk)	1.63±0.4**	<0.0001	0.79 to 2.5	1.63±0.42**	<0.0001	0.79 to 2.46
SBP (mmHg)	-0.08±0.07	0.247	-0.207 to 0.054	0.01±0.092	0.99	-0.18 to 0.18
Apgar score	1.47±0.99	0.14	-0.49 to 3.44	0.33±1.03	0.747	(-)1.7 to 2.38
Preeclampsia	-2.6±2.2	0.234	(-)7.0 to 1.7	0.88±2.88	0.76	(-)4.8 to 6.6
Dose (30mg)	3.4±2.2	0.127	(-)0.93 to 7.7	1.16±2.2	0.604	(-)3.25 to 5.6
Dose (60mg)	-3.5±2.4	0.15	(-)8.3 to 1.3	(-)3.54±2.3	0.123	(-)8.1 to 0.98
Dose (90mg)	-7.2±4.8	0.137	(-)16.8 to 2.3	(-)4.8±4.7	0.302	(-)14.1 to 4.4

SBP; Systolic blood pressure, CI; confidence interval, SE; standard error, ** significant level at p<0.001

Table 3

Univariate and multivariate linear regression model for determining predictors of systolic to diastolic ratio

	Univariate analysis			Multivariate analysis		
Variable	Coefficient β±SE	P-value	95% CI	Coefficient β±SE	P-value	95% CI
Age (yrs)	0.016±0.01	0.25	-0.01 to 0.04	0.007±0.013*	0.046	-0.019 to 0.033
Gestation age (wk)	-0.1±0.02**	<0.0001	-0.14 to (-)0.04	(-)0.1±0.02**	0.005	-0.11 to (-)0.02
SBP (mmHg)	0.02±0.004**	<0.0001	0.01 to 0.03	0.013±0.004**	0.001	0.006 to 0.02

Variable	Coefficient β±SE	P-value	95% CI	Coefficient β±SE	P-value	95% CI
DBP (mmHg)	0.02±0.004**	<0.0001	0.009 to 0.03	(-)0.004±0.008	0.657	(-)0.02 to 0.01
Delivery GA (wk)	-0.16±0.03**	<0.0001	-0.22 to -0.1	(-)0.03±0.04	0.46	(-)0.12 to 0.05
Apgar score	-0.25±0.06**	<0.0001	-0.36 to (-)0.14	(-)0.16±0.06**	0.006	-0.27 to (-)0.05
Preeclampsia	0.43±0.13**	0.001	0.18 to 0.69	(-)0.25±0.19	0.18	(-)0.62 to 0.12
Chronic HTN	-030±0.16	0.076	(-)0.6 to 0.03	(-)0.30±0.14	0.277	(-)0.44 to 0.13

SBP; systolic blood pressure, DBP; diastolic blood pressure, GA; gestation age, HTN; hypertension, SE; standard error, CI; confidence interval, ** significant level at p<0.001, * significant level at p<0.05

Table 4

Univariate and multivariate linear regression model for determining predictors pulsatile index

Variable	Univariate analysis			Multivariate analysis		
	Coefficient β±SE	P-value	95% CI	Coefficient β±SE	P-value	95% CI
Age (yrs)	0.01±0.007	0.12	-0.003 to 0.025	0.009±0.008	0.25	-0.007 to 0.003
Gravidity	0.077±0.03	0.01	0.014 to 0.14	0.07±0.038*	0.02	0.01 to 0.13
Gestation age (wk)	(-)0.03±0.01	0.036	-0.06 to (-)0.002	(-)0.01±0.01	0.44	-0.04 to 0.02
SBP (mmHg)	0.005±0.002	0.017	0.001 to 0.009	0.001±0.003	0.72	-0.004 to 0.006
DBP (mmHg)	0.005±0.002	0.038	<0.001 to 0.009	-0.001±0.005	0.8	(-)0.01 to 0.008
Delivery GA (wk)	(-)0.04±0.02	0.02	-0.07 to (-)0.007	0.016±0.03	0.601	(-)0.04 to 0.08
Apgar scorer	(-)0.07±0.03	0.04	-0.12 to (-)0.005	(-)0.04±0.03	0.21	(-)0.1 to 0.02
Preeclampsia	0.2±0.07	0.003	0.07 to 0.33	0.2±0.07**	0.004	0.06 to 0.32
Chronic HTN	-0.2±0.08	0.03	-0.33 to (-)0.02	(-)0.11±0.08	0.18	(-)0.27 to 0.05

SBP; systolic blood pressure, DBP; diastolic blood pressure, GA; gestation age, HTN; hypertension, SE; standard error, CI; confidence interval, * significant level at p<0.05

Table 5

Univariate and multivariate linear regression model for determining predictors of resistance index

Variable	Univariate analysis			Multivariate analysis		
	Coefficient β±SE	P-value	95% CI	Coefficient β±SE	P-value	95% CI
SBP (mmHg)	0.001±0.001	0.176	<0.001 to 0.002	<0.001±0.001	0.711	-0.002 to 0.001
DBP (mmHg)	0.001±0.001	0.11	<0.001 to 0.003	0.001±0.002	0.68	-0.003 to 0.004
Delivery GA (wk)	-0.01±0.006	0.024	-0.02 to -0.002	-0.005±0.007	0.5	-0.02 to 0.009
Apgar score	-0.02±0.01	0.11	-0.04 to 0.004	-0.01±0.01	0.17	-0.03 to 0.006
PIH	0.07±0.04	0.05	-0.01 to 0.15	0.04±0.04	0.33	-0.04 to 0.11
Preeclampsia	0.05±0.02	0.05	-0.001 to 0.09	-0.01±0.05	0.801	-0.103 to 0.08
Chronic HTN	(-)0.05±0.03	0.11	-0.102 to 0.01	-0.08±0.03*	0.008	-0.13 to 0.02
Dose (30mg)	0.06±0.023	0.01	0.02 to 0.12	0.08±0.02**	0.001	0.03 to 0.13

SBP; systolic blood pressure, DBP; diastolic blood pressure, GA; gestation age, PIH; pregnancy induced hypertension, HTN; hypertension, SE; standard error, CI; confidence interval, ** significant level at $p<0.001$

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