MATERNAL AND PERINATAL OUTCOMES IN HYPERTENSIVE DISORDERS OF PREGNANCY

A DISSERTATION SUBMITTED TO THE PARTIAL FULFILMENT OF THE REQUIREMENTS OF TAMILNADU DR. M.G.R MEDICAL UNIVERSITY FOR THE DEGREE OF MASTER OF SURGERY (M.S) BRANCH VI (OBSTETRICS AND GYNAECOLOGY) EXAMINATION TO BE HELD IN MAY 2022.

REGISTRATION NUMBER : 221916412

CERTIFICATE

This is to certify that the dissertation titled **"MATERNAL AND PERINATAL OUTCOMES IN HYPERTENSIVE DISORDERS OF PREGNANCY"** is the original work of Dr. Monitta M towards the M.S Branch VI (Obstetrics and Gynecology) Degree Examinations of The Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in May 2022.

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CONTENTS

LIST OF ABBREVIATIONS

WHO	- World Health Organization
ISSHP	- International Society for the Study of Hypertension in Pregnancy
ACOG	- American College of Obstetricians and Gynecologists
APLA	- Antiphospholipid antibody
HLA	- Human Leukocyte Antigen
EVT	- Extravillous trophoblast
NK	- Natural killer
HELLP	- Hemolysis, Elevated liver enzymes, Low platelet
ACE	- Angiotensin converting enzyme
DIC	- Disseminated Intravascular Coagulation
ARF	- Acute Renal Failure
AKI	- Acute Kidney Injury
PRES	- Posterior reversible encephalopathy syndrome
VEGF	- Vascular endothelial growth factor
PPH	- Postpartum hemorrhage
FGR	- Fetal Growth Restriction
RDS	- Respiratory distress syndrome
MSAF	- Meconium stained amniotic fluid

MAS - Meconium aspiration syndrome

LBW - Low birth weight

PIH - Pregnancy induced hypertension

IUFD - Intrauterine fetal death

PG E1 - Prostagladin E1

LSCS - Lower segment cesarean section

END - Early Neonatal Death

NICU - Neonatal Intensive Care Unit

HTN - Hypertension

HYPITAT - Hypertension and Preeclampsia Intervention Trial At Near Term

INTRODUCTION

Hypertension has become one of the most common medical problems encountered during pregnancy. It is one of the leading cause for maternal and perinatal morbidity and mortality worldwide. It is of global public health concern both in developed and developing countries. However, the risk that women in developing countries die of complications due to hypertensive disorder of pregnancy is approximately 300 times higher than that for women in developed countries. (1) Hypertensive disorders of pregnancy have a wide spectrum of presentation, ranging from mild elevation of blood pressure to severe hypertension with end organ dysfunctions.

Among the hypertensive disorders, the preeclampsia syndrome, either alone or superimposed on chronic hypertension, is the most dangerous.(2) Eclampsia is the convulsive form of preeclampsia and affects 0.1% of all the pregnancies.(3) Women who developed preeclampsia were three times more likely to progress to eclampsia and if eclampsia develops, they are 14 times more likely to cause maternal mortality.(4) New onset non proteinuric hypertension during pregnancy after 20 weeks of gestation termed as gestational hypertension, is followed by signs and symptoms of preeclampsia almost half the time. Preeclampsia is a complex disorder linked to defective placentation, oxidative stress with release of vasoactive substances, increased thromboxane and cytokine triggered vascular and organ dysfunction.(5) It is not only a severe disorder in pregnancy, but also poses a greater risk of cardiovascular and cerebrovascular events in

future. In the World Health Organization (WHO) systematic review on maternal mortality worldwide, 16 % of maternal deaths were attributed to hypertensive disorders. (6) WHO estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) when compared to developed countries (0.4%).(7)

Hypertension in pregnancy is also a major cause of preterm births resulting in perinatal mortality.(2) Fetuses of hypertensive mothers are also at increased risk for intrauterine growth restriction due to inappropriate placental oxygen transfer.(4)

Prevention of any disease requires a method for prediction of those at high risk for the disorder. Although there are many clinical and biochemical tests like uterine artery Doppler and first-trimester maternal serum markers for prediction of early detection of preeclampsia, there is not enough evidence to suggest their routine use in clinical practice, especially in resource poor settings. This study was conducted to evaluate the maternal and perinatal outcomes in women with hypertensive disorders of pregnancy as it is one of the most common complication in pregnancy leading to adverse maternal and perinatal outcome and this in turn will help to set up protocols and devise various strategies to prevent and reduce such untoward consequences.

AIMS AND OBJECTIVES

Aim:

To study the maternal and perinatal outcomes in hypertensive disorders of pregnancy

Objectives:

Primary Objective:

1. To study the mode of delivery in women with hypertensive disorders of pregnancy

Secondary Objectives:

2. To study the maternal complications in pregnancy complicated by hypertensive disorders

3. To study the perinatal outcomes in women with hypertensive disorders in pregnancy

4. To study the perinatal complications in hypertensive disorders in pregnancy

REVIEW OF LITERATURE

Hypertensive disorders of pregnancy complicates 5 to 10 % of pregnancies globally and it constitutes a major cause for maternal and perinatal morbidity and mortality.(8) According to International Society for the Study of Hypertension in Pregnancy (ISSHP), hypertension is defined as systolic blood pressure 140mmHg or more or diastolic blood pressure 90mmHg or more on atleast two occasions taken four hours apart. (9)

Classification:

Hypertensive disorders in pregnancy are classified into four types according to the American College of Obstetricians and Gynecologists(ACOG) 2013.(10) They are as follows:

- Gestational hypertension
- Preeclampsia and eclampsia
- Chronic hypertension
- Preeclampsia superimposed on chronic hypertension

Gestational hypertension:

When hypertension (Systolic BP of 140mmHg or more or diastolic BP 90mmHg or more) develops for the first time after 20 weeks of gestation, documented on two occasions at least four hours apart in a previously normotensive woman and there is no proteinuria or signs of end-organ dysfunction, it is called gestational hypertension.(11)

It may get reclassified as follows:(11)

-Preeclampsia if proteinuria or new signs of end organ dysfunction develops

-Chronic hypertension, if hypertension persists 12 weeks after delivery

-Transient hypertension, if blood pressure is normal by 12 weeks after delivery

Preeclampsia:

Preeclampsia is defined as new onset hypertension and proteinuria or hypertension and significant end organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman(11).

Proteinuria is defined as (11)

- ≥300mg or more in a 24hour urine sample or
- Spot urinary protein:creatinine ratio of ≥ 0.3 or
- 30mg/dL protein in a random urine sample or
- ≥1+ urine dipstick reading (≥2+ according to ACOG)

Classification of preeclampsia:(10)

Preeclampsia can be further classified into non severe and severe preeclampsia based on the severity of the hypertension and associated end organ changes.

-Nonsevere preeclampsia: The blood pressure is >140/90mmHg but < 160/110mmHg, confirmed by repeat examination after 4 hours, without severe features as described below.

-Severe preeclampsia: The blood pressure is ≥160/110mmHg with proteinuria with or without evidence of multiorgan involvement.

Evidence of organ involvement: (10,11)

Severe headache despite analgesic therapy - Cerebral edema

Photophobia, cortical blindness, scotomata, retinal vasospasm - Changes in optic fundus

Severe and persistent right upper quadrant or epigastric pain - Stretching of liver capsule

Elevated liver enzymes > twice the upper limit of normal range - Liver ischemia

Thrombocytopenia(<100,000/µL) - Platelet aggregation and activation

Serum creatinine >1.1 mg/dL or doubling of the serum creatinine - Impaired renal function

Pulmonary edema - LVF due to hypertension and extravasation of fluid into interstitial space

Eclampsia:

The occurrence of new onset, generalized, tonic clonic seizures or coma in a woman with preeclampsia is called as eclampsia.(12) Seizures may occur antepartum , intrapartum or

postpartum within 48 hours after delivery. Rarely may occur beyond 48 hours postpartum.

Chronic hypertension:

Hypertension (≥ 140/90mmHg) detected before 20 weeks of gestation or that continues beyond 12 weeks postpartum is defined as chronic hypertension.(13)

Preeclampsia superimposed on chronic hypertension:

When there is worsening of preexisting hypertension, new onset proteinuria or worsening of proteinuria in a woman with chronic hypertension, it is referred to as superimposed preeclampsia.(11)

Risk factors for hypertensive disorders of pregnancy:(10,14,15)

Pre-conceptional or chronic risk factors are primi gravida, teenage pregnancy, advanced maternal age, short inter delivery interval, obesity, polycystic ovarian disease, conception with assisted reproductive techniques, past history of pregnancy induced hypertension, family history of hypertension and low socio-economic class.

Underlying medical disorders like renal disease, diabetes, chronic hypertension, connective tissue disorders, antiphospholipid antibody(APLA)syndrome, sickle cell disease, hyperhomocysteinemia, thrombophilia and poorly controlled hyperthyroidism also predisposes to hypertensive disorders of pregnancy.

Exogenous factors like smoking and steroids use and women with pregnancy associated risk factors like multiple gestation and hydatidiform mole are also prone for hypertensive disorders of pregnancy.

Pathophysiology:

Gestational hypertensive disorders are more likely to develop in women with the following characteristics:(16)

- Are exposed to chorionic villi for the first time
- Are exposed to a superabundance of chorionic villi, as with twins or hydatidiform mole
- Have preexisting conditions of endothelial cell activation or inflammation such as diabetes or renal or cardiovascular disease
- Are genetically predisposed to hypertension developing during pregnancy.

Regardless of precipitating etiology, the cascade of events leading to the preeclampsia is characterized by abnormalities that result in vascular endothelial damage with resultant vasospasm, transudation of plasma, ischemic and thrombotic sequelae.(17)

1. Abnormal trophoblastic invasion:

In normal pregnancies, the cytotrophoblast cells of the developing placenta migrate through the decidua and also part of the myometrium to invade both the endothelium and highly muscular tunica media of the maternal spiral arteries, which are the terminal branches of the uterine artery that supply blood to the developing placenta and fetus. As a

result, these vessels undergo transformation from small muscular arterioles to large capacitance, low resistance vessels. Remodeling of the spiral arteries begins in the late first trimester and is completed by around 18 to 20 weeks of gestation, although the exact gestational age at which trophoblast invasion of these arteries ceases is still unclear.(18)

So this remodeling of spiral arteries takes place in two stages as follows:(11)

Stage 1:Invasion of the decidual segment of the spiral arterioles ,which takes place at 10-12 weeks

Stage 2:Invasion of the myometrial segment of the spiral arterioles, which takes place at 16-18 weeks

Thus, normal implantation is characterized by extensive remodeling of the spiral arterioles within the decidua basalis.(16) But in women likely to develop hypertensive disorder, the second stage of myometrial invasion does not take place and cytotrophoblast cells infiltrate the decidual portion of the spiral arteries but fail to penetrate the myometrial segment. Hence the spiral arteries fail to develop into large and tortuous vascular channels which are created by replacement of the musculoelastic wall with fibrinoid material and instead, the vessels remain narrow resulting in placental hypoperfusion. (18)

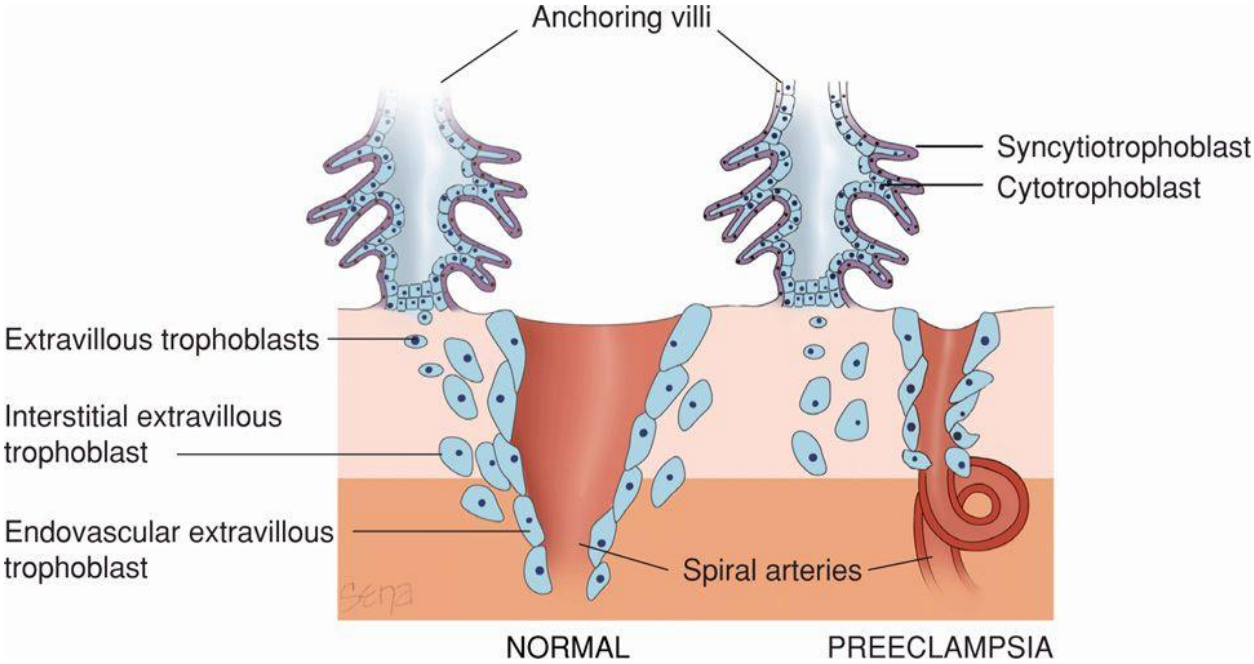


Fig. 1 Abnormal trophoblastic invasion(17)

2. Defective trophoblastic differentiation:

Defective differentiation of trophoblast is one of the possible mechanism responsible for the defective trophoblast invasion of the spiral arteries.(19) Trophoblast differentiation during the endothelial invasion involves alteration in expression of various different classes of molecules, including cytokines, extracellular matrix molecules ,adhesion molecules, metalloproteinases and the class Ib major histocompatibility complex molecule, HLA-G.(20,21)

During normal differentiation, a process known as pseudo-vasculogenesis takes place. In that, the invading trophoblasts alter their adhesion molecule expression from those that are characteristic of epithelial cells (integrin alpha6/beta1, alphav/beta5 and E-cadherin) to those of endothelial cells (integrin alpha1/beta1, alphav/beta3, and VE-cadherin).(22)

The trophoblasts attained from the women with preeclampsia do not show the upregulated adhesion molecule expression or pseudo-vasculogenesis.(18)

In women with severe preeclampsia, transcriptomics and culture studies using human trophoblasts have suggested that semaphorin 3B may be a candidate protein that inhibits vascular endothelial growth factor signaling and thus contributing to the impaired trophoblast differentiation and invasion.(23)

3. Placental hypoperfusion and hypoxia

Placental hypoperfusion appears to be both a cause and a consequence of abnormal placental development.(18) The failure of throphoblastic invasion and vasodilatation results in placental hypoperfusion and the resultant ischemia and hypoxia leads to release of syntiotrophoblast debris and microparticles leading to production of cytokines, tumour necrosis factor-alpha and interleukins which in turn leads to oxidative stress and maternal vascular endothelial inflammation and damage.

Medical conditions associated with vascular insufficiency like hypertension, diabetes, renal disease, systemic lupus erythematosus, inherited and acquired thrombophilias also increase the risk of abnormal placentation and preeclampsia.(24) Obstetric conditions like hydatidiform mole, twin and triplet gestation can also cause relative placental ischemia because of the increase in placental mass without correspondingly increasing placental blood flow, thus increasing the risk of preeclampsia.(24,25)

4. Immunological factors

Trophoblastic cells are the only fetus-derived cells which are in direct contact with maternal tissues and blood. Fetal syncytiotrophoblast synthesizes and secretes various factors that regulate the immune responses of maternal cells both at the implantation site and systemically. (26) Normal implantation depends on the controlled trophoblastic invasion of maternal decidua and spiral arteries (27) and there is an immunological tolerance to paternal and fetal antigens ,thus facilitating placental implantation and continuation of pregnancy.(11)

Immunologic abnormalities which are similar to those observed in organ rejection, have been observed in preeclamptic women.(28) The extravillous trophoblast (EVT) cells express an unusual combination of HLA class I antigens namely HLA-C, HLA-E, and HLA-G. The Natural killer (NK) cells that express a variety of receptors (CD94, KIR, and ILT) known to recognize class I molecules, infiltrate the maternal decidua in close contact with the EVT cells.(29) The interaction between the NK cells and EVT cells has been hypothesized to control the placental implantation. In preeclampsia, the conflict between the maternal and paternal genes is believed to induce abnormal placental implantation through increased NK cell activity.(18)

Dendritic cells are cells that present antigens to T cells and they play an important role in the development of a receptive endometrium for implantation.(26) Placental bed biopsies from preeclamptic women have revealed increased dendritic cell infiltration in the decidual tissue. (30) As dendritic cells are an important initiator of the antigen-specific T-cell responses to transplantation antigens, it is possible that increased number of dendritic

cells can result in alteration in the presentation of maternal and fetal antigens at the decidual level, which may lead to either abnormal implantation or altered maternal immunologic response to fetal antigens.(18)

5. Genetic factors

From a hereditary viewpoint, preeclampsia is a multifactorial, polygenic disorder.(17) Genes for antiangiogenic factors are present in chromosome 13 and genes on chromosome 12q are linked to HELLP syndrome. Placental changes develop in women with susceptible genes(11). Ward and Taylor (2014),in their comprehensive review, cite an incident risk for preeclampsia of 20 to 40 percent for daughters of preeclamptic mothers, 11 to 37 percent for sisters of preeclamptic women and 22 to 47 percent for twins.(31)

The hereditary predisposition for preeclampsia likely arises from interactions of hundreds of inherited genes which are both maternal and paternal, that controls a myriad of enzymatic and metabolic functions throughout every organ system.(32)

GENE(POLYMORPHISM)	FUNCTION AFFECTED
MTHFR(C677T)	Methylene tetrahydrofolate reductase
F5(Leiden)	Factor V Leiden
AGT(M235T)	Angiotensinogen
HLA(Various)	Human leukocyte antigens
NOS3(Glu 298 Asp)	Endothelial nitric oxide
F2(G20210A)	Prothrombin (factor II)
ACE (I/D^{at} Intron 16)	Angiotension-converting enzyme
CTLA4	Cytotoxic T-lymphocyte-associated protein
LPL	Lipoprotein lipase
SERPINE1	Serine peptidase inhibitor

Tab.1 Genes with possible associations with preeclampsia(17)

6. Maternal vascular endothelial dysfunction

In normal pregnancy there is a balance of proangiogenic factor production like vascular endothelial growth factor and placental growth factor and antiangiogenic factor production like soluble fms-like tyrosine kinase-1. But in preeclampsia, the placental hypoperfusion and the resultant hyopxia lead to an increase in the production of antiangiogenic factors and a decrease in proangiogenic factors, resulting in endothelial

damage and dysfunction. The damaged endothelium serves a nidus for platelet aggregation and microvascular coagulation.(11)

7. Metabolic factors

Central obesity and insulin resistance are risk factors for preeclampsia. Free fatty acids and triglycerides increase in preeclampsia probably due to insulin resisitance. Hyperlipidemia and oxidative stress resulting in free oxygen radicals producing lipid peroxidation results in endothelial dysfunction. (33)

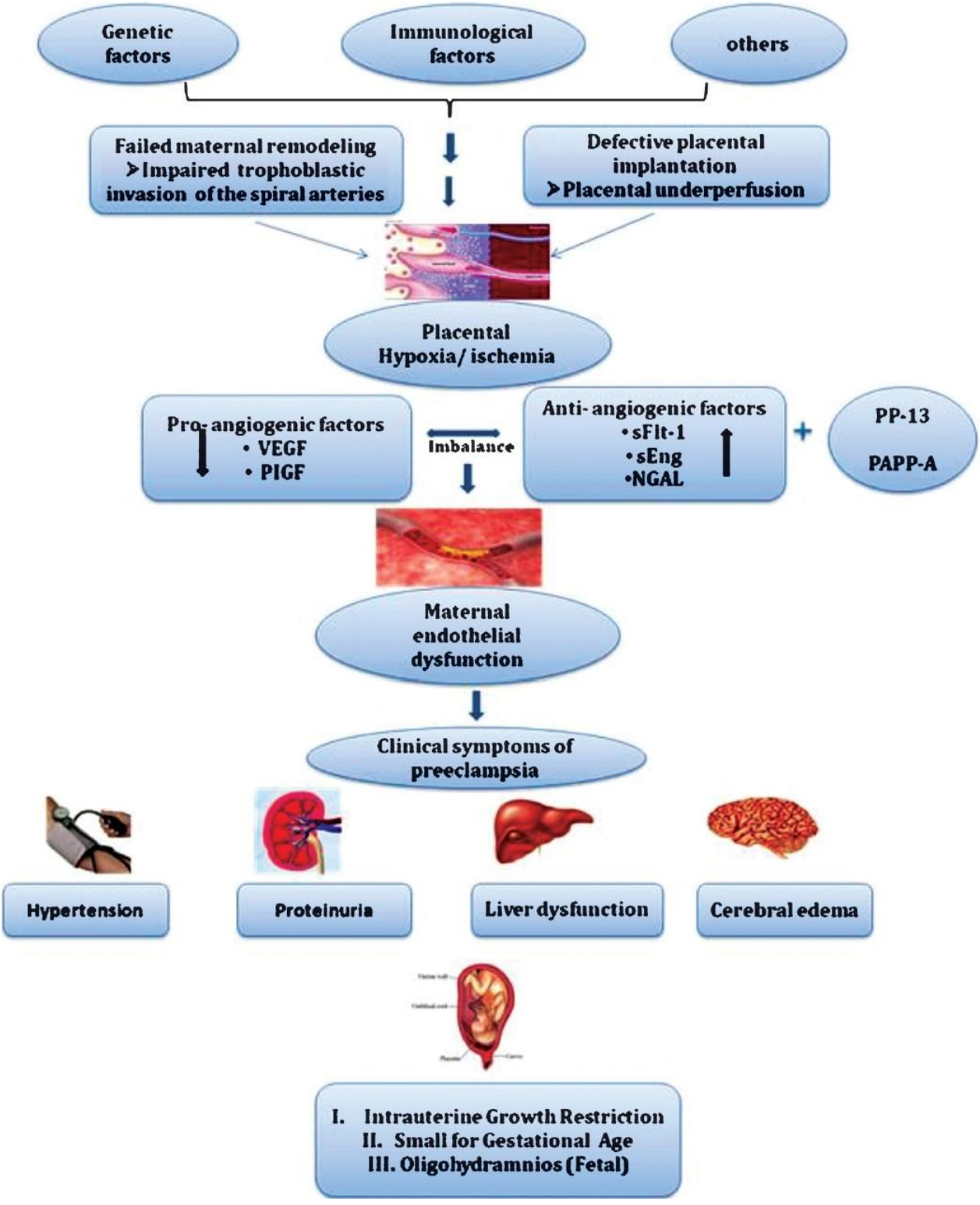


Fig.2 Pathogenesis of preeclampsia(6)

Management:

The main goals of management are as follows:

1. Early recognition of worsening of the disease

2. Close monitoring of the mother and the baby

3. Appropriate timing of delivery

4. Appropriate mode of delivery

Management of hypertensive disorders of pregnancy without severe features:

Hypertensive disorders in pregnancy without evidence of severe features are considered to be consistent with mild disease. Hence management guidelines are applicable to gestational hypertension, preeclampsia and superimposed preeclampsia not associated with any symptoms or laboratory abnormalities consistent with severe features.(34)

Antenatal monitoring of hypertensive women includes both fetal monitoring and maternal evaluation. All women diagnosed with hypertension in pregnancy should have a complete blood count, serum creatinine, liver enzymes, 24-h urine collection or urine protein to creatinine ratio to assess urine protein once weekly. Symptoms and serial blood pressure should be monitored twice weekly with adequate patient education to access care immediately on development of any severe feature.

Fetal assessment should be done through ultrasonographic evaluation for fetal growth every 2 to 3 weeks along with nonstress test once weekly for women with gestational hypertension and twice weekly for women with preeclampsia without severe features.

Pharmacological therapy is indicated if blood pressure remains above 140/90mmHg, aiming to keep blood pressure at 135/95mmHg or less. (34,35)

Indications for delivery per the Task Force for mild gestational hypertension and preeclampsia without severe features are as follows:

- 37 weeks of gestation or more
- Suspected abruptio placenta
- 34 weeks of gestation with any of the following:
    - Progressive labor or rupture of membranes
    - Estimated fetal weight less than fifth percentile on ultrasound
    - Oligohydramnios (amniotic fluid index less than 5 cm)
    - Persistent biophysical profile of 6/10 or less.

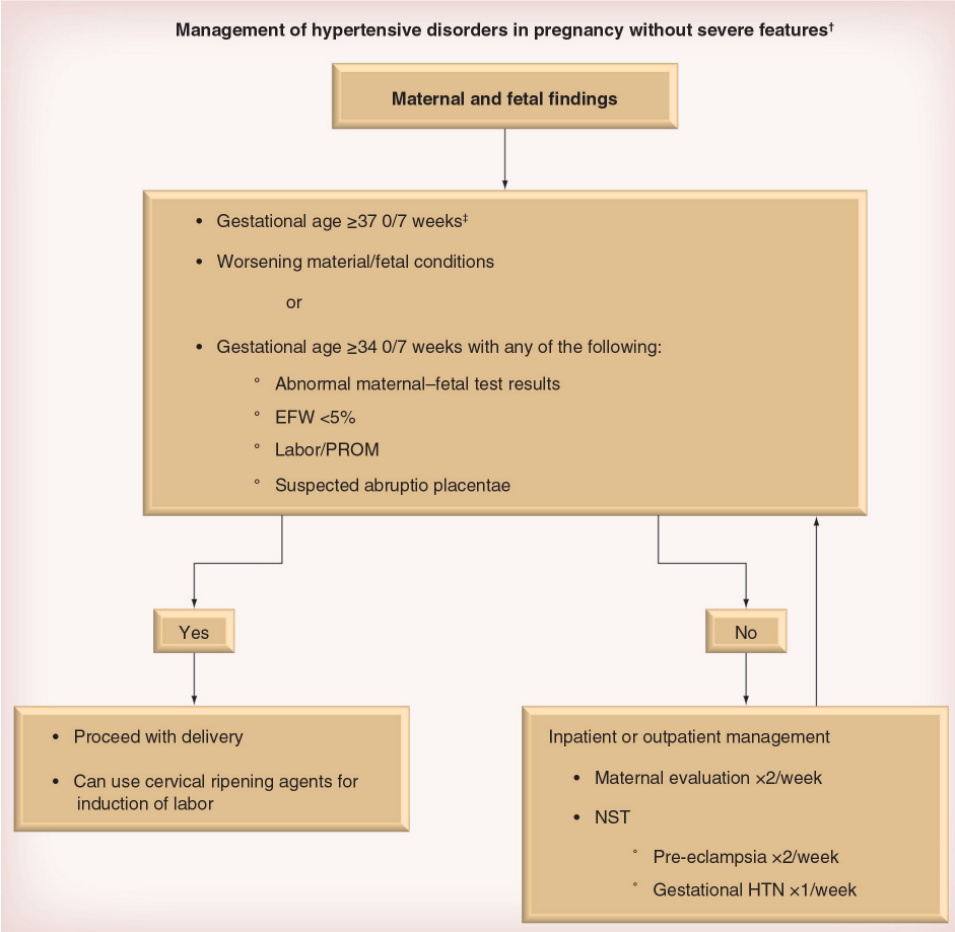


Fig. 3 Management of hypertensive disorders of pregnancy without severe features(34)

Mode of delivery:

Ripening of cervix with prostaglandins and induction of labour with amniotomy followed by oxytocin use is safe. Caesarean section is indicated only for obstetric reasons.(11)

Management of chronic hypertension in pregnancy:

Preconception counseling and management includes evaluation for the etiology of hypertension, identification of any end organ damage, adequate control of blood pressure prior to conception and conversion of ACE inhibitors or angiotensin II receptor blockers

to antihypertensive agents which are safe in pregnancy. Laboratory investigations include urinalysis, renal function test, 24-h urine collection for total protein loss and creatinine clearance and liver function test. The Task Force suggests physician referral if secondary hypertension is suspected.(34)

As systematic reviews demonstrate the significant reduction in developing preeclampsia by 17% at the use of low dose aspirin, women with chronic hypertension should be started on aspirin 75–150 mg once daily from 12 weeks and should be seen in weekly appointments if hypertension is poorly controlled and every 2 to 4 weeks if hypertension is well controlled. (35)

As the risk of fetal growth restriction is higher in pregnant women with chronic hypertension, fetal surveillance with ultrasonography is essential. If any evidence of fetal growth restriction is found, assessment of the fetoplacental status is recommended using umbilical artery velocimetry.

The goals of management in chronic hypertension include minimizing the fetal risks attributable to hypertension, development of vascular disease and the possible harmful effects of antihypertensive agents causing decreased uteroplacental perfusion.(34)

Timing of delivery:

The recommended gestational age for delivery is 38 weeks in a woman with chronic hypertension.(34) However ACOG suggested the following timing of delivery women with chronic hypertension : (36)

• ≥38 to 39+6 weeks of gestation for women not requiring medication

• ≥37 to 39 weeks for women with hypertension controlled with medication

• 34 to 36+6 weeks for women with severe hypertension that is difficult to control

Management of hypertensive disorders in pregnancy with severe features:

Severe features are associated with higher pregnancy complications and thus are consistent with severe disease regardless of the diagnosis of hypertension (gestational, preeclampsia or superimposed preeclampsia).(34) Once a woman has features of severe disease, she must be admitted, evaluated and stabilized. Antihypertensives, corticosteroids (if gestational age is between 26 and 34 weeks) and seizure prophylaxis using magnesium sulfate should be started as early as possible.(11)

Maternal evaluation includes monitoring blood pressure half hourly, urine output hourly, urine protein by dipsick 4 hourly and other investigations include urine protein:creatinine ration, peripheral smear for schistocytes, liver enzymes, platelet count, serum LDH and serum creatinine. Fetal evaluation includes nonstress test, ultrasonagraphy to assess biophysical profile, estimated fetal weight and umbilical artery Doppler.(11)

Beyond 34 weeks, for women with severe preeclampsia, immediate delivery is recommended.

For women with severe preeclampsia at ≤ 34 weeks of gestation but beyond the period of viability, the administration of corticosteroids for fetal lung maturity is recommended as mentioned earlier and expectant management can be considered only at facilities with adequate maternal and neonatal intensive care units. But delivery cannot be delayed regardless of gestational age if maternal condition is complicated by uncontrollable

severe hypertension, eclampsia, HELLP syndrome, pulmonary edema, abruptio placentae, disseminated intravascular coagulation or there is evidence of nonreassuring fetal status or fetal demise.(34)

For women with severe preeclampsia before the period of fetal viability, Task Force recommends delivery after maternal stabilization and expectant management is not recommended.(34)

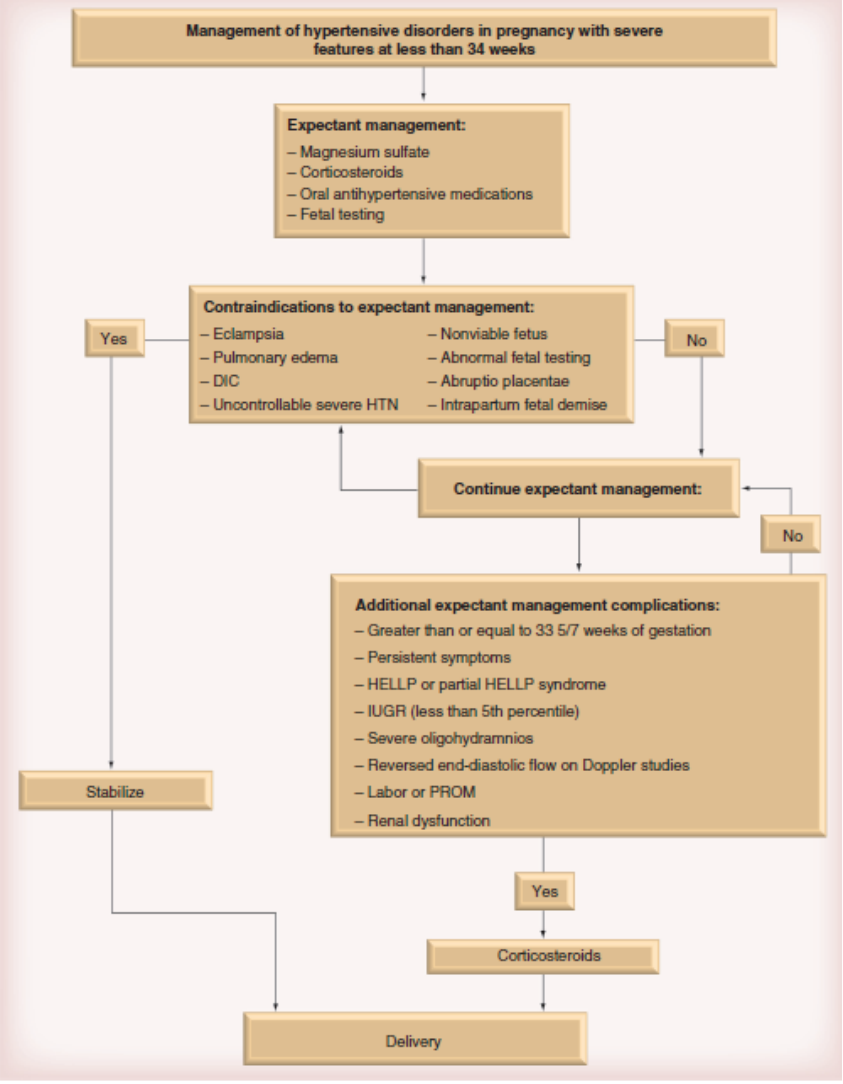


Fig. 4 Management of hypertensive disorders of pregnancy with severe features(34)

Mode of delivery:

Decision regarding the mode of delivery should be taken after considering the gestational age and favorability of the cervix. The second stage of labour should be cut short by instrumental delivery.(11)

Antihypertensive agents used in pregnancy:(37)

Drug	Dose	Action	Contraindications	Practise Points
Methyl dopa Clonidine	250-750mg tds 75-300µg tds	Central	Depression	Slow onset of action over 24 hours, dry mouth, sedation, depression, blurred vision Withdrawal effects: rebound hypertension
Labetalol Oxprenolol	100-400mg q8h 20-160 mg q8h	β blocker with mild alpha vasodilator effect β blocker with intrinsic sympathomim etic activity	Asthma, chronic airways limitation	Bradycardia, bronchospasm, headache, nausea, scalp tingling (labetalol only) which usually resolves within 24 hours
Nifedipine	20mg -60 mg slow release bd	Ca channel antagonist	Aortic stenosis	Severe headache in first 24 hours Flushing, tachycardia, peripheral oedema, constipation
Prazosin	0.5-5 mg q8h	α blocker		Orthostatic hypotension especially after first dose
Hydralazine	25-50 mg q8h	Vasodilator		Flushing, headache, nausea, lupus-like syndrome

Tab. 2 Antihypertensive agents

Postpartum management:

In all women with gestational hypertension, preeclampsia and superimposed preeclampsia, blood pressure should be monitored in the hospital or equivalent outpatient surveillance should be performed for at least 72 hours postpartum and after 7 to 10 days of delivery or earlier in women with symptoms. (34)Also magnesium sulphate is usually continued for 24 hours postpartum in women with severe preeclampsia but in women having preeclampsia without severe features, therapy can be safely discontinued after 12 hours.(38) In women with eclampsia, it is continued for 24 hours post delivery or 24 hours after the last seizure, whichever occurs later.(11) As the blood pressure normalizes gradually, the dose of antihypertensives should be titrated accordingly. Even in the absence of intrapartum treatment, postpartum antihypertensive therapy may be indicated in women with chronic hypertension before and during pregnancy.(34)

MODE OF DELIVERY:

While associated with greater than average rates of Cesarean section, the presence of a hypertensive disorder complicating a woman's pregnancy is not an automatic indication for Cesarean delivery.(39) The potential maternal and fetal benefits to be achieved by labour induction is to be carefully considered against the requirements for emergency or urgent delivery. For women with any type of hypertensive disorder of pregnancy, vaginal delivery should be considered unless a Caesarean delivery is required for other obstetric indications. The rate of successful induction of labour with vaginal delivery is 47.5% at 28–32 weeks and 68.8% at 32–34 weeks of gestation.(39)

In a prospective observational study by Devi et al among 180 women with hypertensive disorders of pregnancy,50%(n=90) underwent normal vaginal delivery, 10%(n=18) underwent instrumental delivery and 40% (n=72) underwent LSCS (8) and in another retrospective study by Joshi et al among 120 women with hypertensive disorders of pregnancy, majority of women 67.5% (n=81) had vaginal delivery and 32.5% (n=39) underwent LSCS. (40)

On the contrary, the rate of Cesarean section in pregnant women with hypertensive disorders was 60.22% according to Ramos Filho et al in a study among 4,464 women with hypertensive disorder of pregnancy (41) and it was 68% and 78 % among women with severe preeclampsia according to Katz et al and Dissanayake VH et al respectively. (42,43) Many other studies also reported high LSCS rate, primarily among women with severe preeclampsia and eclampsia. Among women with eclampsia, 71% LSCS rate was reported by Miguel M et al.(44) 64.5% LSCS rate was reported by Pillai and 72% by Tufnell et al among women with severe preeclampsia and eclampsia.(45,46)

In a study by Corrigan et al among 3531 women with hypertensive disorder of pregnancy, 37.8% had normal vaginal delivery,16.8 % had instrumental delivery and 45.4% had caesarean section .(47) In the same study, 94.1 % women with severe preeclampsia, 68.8 % women with eclampsia and 73.6 % women with HELLP syndrome had cesarean section.(47)Thus rate of cesarean section tends to increase with the severity of hypertension.

Yucesoy et al also noted 41.2 % women with hypertensive disorder delivered by vaginal route and 58.8% by caesarean section. Fetal distress was the most common indication for

cesarean section(46%) followed by previous cesarean section (10.6%), malpresentation (9.3%), nonprogressive labour(8.6%), placental abruption (8%), multiple pregnancy (4%), abnormal doppler examination findings (4%), cephalopelvic disproportion (3.3%), deteriorating medical condition (2%), elective (2%) and placenta previa (1.3%) .(48)

COMPLICATIONS:

1. MATERNAL COMPLICATION

HELLP SYNDROME AND PARTIAL HELLP

HELLP syndrome i.e hemolysis, elevated liver enzymes and low platelet count is a severe complication of hypertensive disorder of pregnancy. It is defined by the presence of all the following three criteria.(15)

-Hemolysis (Schistocytes or red cell fragments on peripheral smear, LDH ≥ 600U/L, Total serum bilirubin ≥1.2mg/ml)

-Elevated liver enzymes(> twice the upper limit of normal range)

-Low platelet count(<1,00,000/μl)

HELLP syndrome was first suggested by Weinstein in 1982 (49) and partial HELLP Syndrome is the presence of one or two features of HELLP syndrome.(50)

HELLP syndrome in general complicates 0.2-0.6% of all pregnancies but its incidence increases to 4-12% in severe preeclampsia.(51) In a study by Devi et al, among 180 women with hypertensive disorders of pregnancy,5 (2.7%) had HELLP syndrome(8) and Kolluru et al observed HELLP syndrome in 3.4 %(n=8) of women in a study with 234

women with gestational hypertension(52) whereas 12.5%(n=15) of women developed HELLP syndrome among 120 women with hypertensive disorders of pregnancy as observed by Josh et al(40).

In a prospective comparative study by Pairu et al among women with gestational hypertension and women with preeclampsia, 3(2.5%) out of 120 women with preeclampsia , developed HELLP whereas among 100 women with gestational hypertension, none developed the syndrome.(5) Somro et al ,out of 112 women with hypertensive disorder of pregnancy, observed that 2 (1.8%) of women developed HELLP syndrome(53) and C.S.Madkar et al found 2 women with HELLP syndrome(0.8%) among 250 women with hypertensive disorder of pregnancy (54)

In about 70% of the patients, HELLP syndrome develops before delivery with a peak frequency between 27th and 37th gestational weeks. In the postpartum period, HELLP syndrome usually develops within 48 hours in women with hypertensive disorder of pregnancy.(51)

Nevertheless, HELLP Syndrome is a life threatening condition if not acted upon promptly. A clinical study conducted by Dan Di et al in China to describe the outcomes of obstetric patients with concurrent eclampsia and HELLP syndrome showed that maternal death was 35% with concurrent eclampsia and HELLP syndrome which was significantly higher than the rate in eclampsia without HELLP syndrome(3%). (55) In an analytical cross sectional study among 451 women with hypertensive disorder of pregnancy by Dassah et al, maternal death was 10,among which cause of death was HELLP syndrome in one of the women.(56)

PLACENTAL ABRUPTION

Placental abruption refers to partial or complete placental detachment in pregnancies over 20 weeks of gestation prior to delivery of the fetus.(57)

As high blood pressure increases the risk of bleeding into the decidua basalis and the separation of the placenta, risk of abruption increases with the hypertensive disorders of pregnancy. In 40–50% of women with abruptio placentae there is underlying hypertension(58)

Chronically hypertensive patients were more than three times likely to develop placental abruption (odds ratio 3.13, 95% confidence interval 2.04-4.80) as compared to normotensive patients and the OR for placental abruption was 1.73 (95% CI 1.47-2.04) for patients with preeclampsia in a study by Ananth et al . (59)

The incidence of abruption was 3.3% (n=6) among 180 women with hypertensive disorders of pregnancy as observed by Devi et al in a prospective observational study and 7.5%(n=19 out of 255 women) as analysed by Yucesoy at al(48) whereas it was as high as 16.9% in a study by Soomro et al. (60)

The incidence of abruption is slightly higher in preeclampsia when compared to chronic or gestational hypertension. Pairu et al in a prospective comparative study of maternal and perinatal outcome in pregnancy induced hypertension and preeclampsia showed incidence of abruption to be 1% among PIH women and 1.6% among preeclamptic women.(5)

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation is a systemic process with the potential for causing thrombosis and hemorrhage.(61) It was first described by Joseph DeLee in 1901 as a fatal hemorrhagic diathesis following placental abruption. (62)

The pathophysiology in DIC is the systemic activation of the coagulation cascade leading to extensive fibrin deposition and subsequent microvascular thrombosis. Furthermore with the consumption of platelets and coagulation factors leads to chances of severe bleeding.(62)

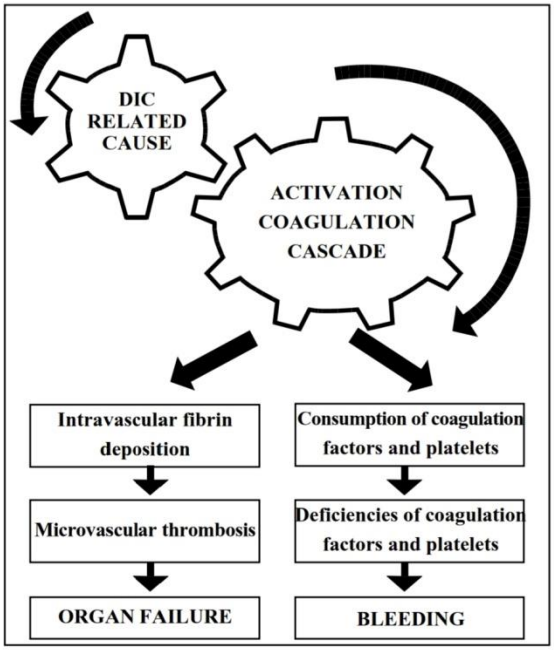


Fig. 5 Pathophysiology of DIC(62)

Normal coagulation pathway:

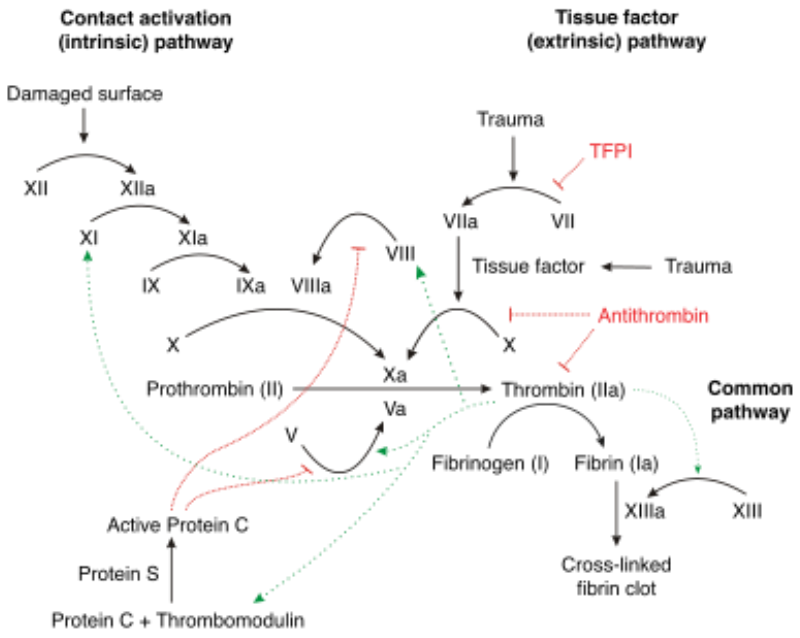


Fig.6 Coagulation pathway(63)

Pathogenesis in hypertensive disorder of pregnancy:

- Preeclampsia and HELLP syndrome: Endothelial injury
- Placental abruption: Large amounts of thromboplastin at the site of abruption

Incidence of DIC was found to be 1.1%(n=2) among 180 women with hypertensive disorder of pregnancy by Devi et al (8) , 2.35%(n=6) in a study by Yucesoy et al among 255 pregnant women with hypertension (48) and 5%(n=6) among 120 women with pregnancy induced hypertension in a retrospective study by Joshie et al.(40)

ACUTE RENAL FAILURE

Acute renal failure was regarded as relatively uncommon in preeclampsia and eclampsia and if it occurs it is usually of moderate degree or reversible.(64) But recent data indicates that the incidence of acute renal failure is increasing, with hypertensive and thrombotic microangiopathic disorders of pregnancy being the major contributors to the burden of ARF.(65)

The incidence of ARF by various studies ranged between 1.2-3.3%(8,40,48,52) but it was as high as 6.2%(n=7) among 112 women with hypertensive disorder of pregnancy in a prospective observational study by Soomro et al.(60)

The American College of Obstetricians and Gynecologists defines renal insufficiency in the setting of hypertensive disorders of pregnancy as a serum creatinine level >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of renal disease(65)

Various histological and functional changes occur in the renal system in hypertension as follows:

- Swelling of endothelial cells of the renal glomeruli leads to obstruction of the lumen of the capillaries which is known as glomerular capillary endotheliosis - the characteristic histological renal lesion in preeclampsia
- The glomeruli are enlarged and hence have markedly decreased blood flow
- Glomerular filtration is decreased due to

  (a) Reduction in renal blood flow due to high resistance

  (b) Reduced plasma volume

  (c) Glomerular capillary endotheliosis

- Increased permeability of glomeruli to proteins results in proteinuria
- Serum creatinine levels increase due to reduction in glomerular filtration rate and creatinine clearance
- Uric acid levels increase due to reduced clearance of uric acid by the kidney because of renal tubular dysfunction.(11) It is also due to placental ischemia leading to increased trophoblastic turnover and increased production of purines.(33)
- Activation of renin-angiotensin system leads to reduced excretion of sodium and chloride resulting in sodium retention

In case of profuse bleeding, hypotension and hypovolemia, acute tubular and cortical necrosis can occur. Cortical necrosis is usually reported as rare but in a study by Stratta et al, cortical necrosis was seen in 29.4% women with hypertensive disorder of pregnancy. Moreover the severity of renal impairment was not seen to be to be related to chronological age, parity, period of pregnancy in which preeclampsia commenced, presence of eclampsia or the concomitance of earlier vascular or renal disease. The superimposition of abruptio placentae was the only clinical factor significantly correlated with cortical necrosis (p greater than 0.05). (64)

The association between preeclampsia, eclampsia and placental abruption seemed to have unfavorable prognostic sign for the kidney owing to the contribution of additional damage mechanisms like vasospasm, disseminated intravascular coagulation, hemorrhagic shock furnished by placental abruption as well.(64)

Multiple studies have demonstrated that AKI is a risk factor for maternal death in patients with HELLP syndrome and one among them showed AKI in the setting of HELLP syndrome carried an 11.5% maternal mortality rate(66)

Irreversible renal damage was seen in 7% of patients with HELLP syndrome according to a study by Yilmaz et al(66). In a study by Conti-Ramsden et al, pregnancy-related AKI complicated approximately 15% of admissions with preeclampsia and over half of them were severe (stage 2 or 3 AKI) with high rates of associated maternal (3.0%) and perinatal (37.1%) mortality. History of a previous hypertensive disorder of pregnancy was the most significant risk factor for development of AKI and worsening AKI severity as well. It also showed that approximately two-thirds of women had recovered from AKI at time of discharge.(67)

ACUTE RESPIRATOTY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a state of diffuse inflammatory lung injury characterized by acute onset, non cardiogenic pulmonary edema with hypoxemia as defined by an arterial partial pressure of oxygen-to-inspired oxygen ratio of under 300.(68)

The pregnant state may predispose to the development ARDS by various mechanisms, including the increased circulating blood volume, the reduced serum albumin level,a possible upregulation of components of the acute inflammatory response and increased capillary leak.(68)

The frequency of ARDS in preeclampsia or eclampsia was 22.1% and in gestational hypertension was 10.2% according to study conducted by Rush et al.(68) ARDS in preeclampsia may be due to the activation of the inflammatory process in preeclampsia (69).In a study by Mabie. C et al to determine the causes of ARDS in pregnancy found 25% women with preeclampsia or eclampsia had ARDS complication.(70)

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome characterized by signs and symptoms like headache, seizures, altered mental status and visual loss. It is also characterized by white matter vasogenic edema affecting the posterior occipital and parietal lobes of the brain predominantly.(71) PRES was first described in 1996 by Hinchey et al.(72)

It is also known as acute hypertensive encephalopathy or reversible posterior leukoencephalopathy which is a neurotoxic state that occurs secondary to the inability of the posterior circulation to autoregulate in response to acute changes in blood pressure. (73)The cerebral edema and symptoms are often reversible, although permanent parenchymal injury and clinical disability can occur in severe cases.(74)

Pathophysiology:

- The exact pathophysiological mechanism of PRES is still unclear.
- Three hypotheses which have been proposed till now, are as follows:

  (i) Cerebral vasoconstriction causing subsequent infarcts in the brain

  (ii) Failure of cerebral autoregulation with vasogenic edema

-The ability of the brain to maintain a constant blood flow despite changes in perfusion pressure is called cerebral auroregulation. When the differences between the cerebral intraarterial pressure and the cerebral venous pressure rises higher than 160mmHg, autoregulation is lost and the cerebral blood flow depends on the mean arterial pressure.(33)

-When cerebral pressure increases the cerebral vessels dilate and cerebral vascular resistance decreases thus leading to huge increase in cerebral blood flow and hypertensive encephalopathy.(33)

(iii)Endothelial damage with blood–brain barrier disruption further leading to fluid and protein transudation in the brain

Eclampsia is strongly associated with PRES. A retrospective cohort study of 47 patients diagnosed with eclampsia at a single center found radiographic evidence of PRES in 46 patients (97.9%).(75) Similarly, another study by Wagner et al found clinical and radiologic findings of PRES in all women with eclampsia, concluding that the clinical syndrome of eclampsia is associated with an anatomical substrate that is recognizable by neuroimaging as PRES. (76)

The changes in subcortical regions in MRI were comparable to those of PRES in most of patients (≥80%) having severe preeclampsia combined with headache according to Chao et al. The study also found that Susceptibility-weighted images(SWI) could identify microhemorrhage in patients and prompt management could prevent deterioration into eclampsia or stroke.(77)

PULMONARY EDEMA

Pulmonary edema is a feature of the severe end of the disease spectrum and was observed in approximately 10 percent of 63 cases of preeclampsia with severe features in a prospective study(14). The etiology of pulmonary edema in preeclampsia is multifactorial.

Following are the major changes in the cardiovascular system:

- Increase in cardiac afterload caused by hypertension
- Endothelial cell activation with increased capillary permeability which leads to extravasation of fluid from the intravascular space into the extracellular space and into the lungs resulting in pulmonary edema(33)
- Extravasation of plasma into the interstitial space and vasoconstriction leads to hemoconcentration, due to which women with preeclampsia are senstitive to vigorous fluid therapy and acute blood loss and are at risk of pulmonary edema and hypotension
- Proteinuria and the resultant hypoalbuminemia leads to reduction in plasma oncotic pressure, which also increases the risk of pulmonary edema
- Decrease in capillary volume expansion due to vasospasm and shrinkage of the intravascular compartment(78)

Pulmonary edema could be due to a combination of these factors. However, it is thought that increased systemic vascular resistance induces significant changes in loading conditions of the ventricular myocardium contributing to diastolic filling abnormalities

and to the development of an ischemic substrate with the potential for development of heart failure, pulmonary edema and/or sudden death. (79)

A retrospective review by Thornton et al demonstrated that acute pulmonary oedema in hypertensive pregnant women was strongly associated with increased use of intravenous fluid administration in the units that have unrestricted fluid policies for women during labor, cesarean section and magnesium sulphate seizure prophylaxis.(80)

Preeclampsia can result in pulmonary edema, the incidence being 2.9% according to Sibai et al. and it was more common in obese and chronically hypertensive women.(81) This problem most commonly occurs in the early postpartum period, related to fluid administration as mentioned earlier and return of blood to the central circulation as the uterus contracts.(69) Among women with preeclampsia, higher risk for pulmonary edema was observed in relation to markers of more severe preeclampsia, including lower platelet count, higher serum uric acid concentration, and receipt of magnesium sulphate whereas multiparity was associated with a lower risk of pulmonary edema(82)

Pulmonary edema was seen in 1.1% among 180 pregnant women with hypertension in a study by Devi et al(8) whereas it was 6.2% among 112 women with hypertensive disorder of pregnancy in a study done by Soomro et al with maximum in women with eclampsia (60)

Early aggressive blood pressure treatment can reduce the risk of pulmonary edema and thus, continuous monitoring would be relevant for early diagnosis and management, especially among nulliparous preeclamptic women with multifetal pregnancies.(83)

CEREBROVASCULAR ACCIDENT

Cerebrovascular disease is one of the leading cause of maternal mortality in women with preeclampsia, with the majority of deaths caused by intracerebral hemorrhage(84). Cerebral hemorrhage was noted in 0.8%(n=2) women among 234 pregnant women according to Kolluru at al and 1.1%(n=3) out of 255 women with hypertensive disorder of pregnancy in a study by Yucesoy et al.

Hypertensive disorders of pregnancy serve as risk factors for both ischemic and hemorrhagic strokes in pregnancy, with hemorrhagic strokes being the majority. The maternal cerebral vasculature is highly vulnerable to adverse effects of preeclampsia. Moreover, preeclampsia shares common pathophysiology and risk factors with stroke including endothelial dysfunction, dyslipidemia, hypertension, hypercoagulability and abnormal cerebral vasomotor reactivity. Inflammation, oxidative stress, and hypoxia-induced angiogenic factors including sEng (soluble endoglin) and sFlt-1 (soluble fms-like tyrosine kinase-1), VEGF (vascular endothelial growth factor) inhibitor, all play important roles in the maternal vascular damage seen in preeclampsia.(84) The risk of acute cerebrovascular disease in pregnancies complicated by preeclampsia is as high as 1 in 500 deliveries according to a study by Miller et al. Infections, chronic hypertension, coagulopathies and underlying prothrombotic conditions increase pregnancy associated stroke risk in women with preeclampsia. (85)

Nationwide Inpatient Sample epidemiological study of stroke in pregnancy, also showed preeclampsia and eclampsia being associated with a four fold increased risk of stroke(86)

and accounts for 5%–12% of overall maternal mortality.(87) Soomro et al found 2.6% women with cerebrovascular accident and all of them had eclampsia.(60)

The effects of preeclampsia on the maternal brain appear to continue for years past the initial injury. Women with a history of preeclampsia had 3 times higher chance of having abnormally high carotid intima-media thickness, which is a marker of subclinical atherosclerosis highly associated with future stroke. Also women with a history of preeclampsia have increased white matter hyperintensities on MRI, which is a marker of cerebral small vessel disease that is highly associated with stroke and dementia. Prior preeclampsia is an independent risk factor for future stroke in women as well.(84) The same was found by Wang et al that pregnant women with hypertension were are at 2-fold increased risk for future stroke.(88)

POSTPARTUM HEMORRHAGE

Postpartum hemorrhage is defined as bleeding that occurs within 24 hours after delivery and that results in blood loss ≥500ml following a vaginal delivery and of ≥ 1000ml following a caesarean section.(89)

Bleeding after delivery of the placenta is normally controlled by myometrial contraction and local decidual hemostatic factors such as plasminogen activation inhibitor, circulating clotting factors and platelets. Failure of any of these mechanisms results in hemorrhage.

Women with preeclampsia have a 1.5 fold increased risk for postpartum haemorrhage.(90). Irrespective of onset of labour or mode of delivery, preeclampsia has increased risk for PPH(90)

Severe preeclampsia and HELLP syndrome were found to be two strongest risk factors for severe PPH according to a study by Nyfløt et al.(91)

Soomro et al found 27.6%(n=31) women with PPH among 112 women with hypertensive disorder of pregnancy accounting to the most frequent maternal complication encountered(60), whereas only 1.2% had PPH according to a study by Kolluru et al(52) and 6.1% in a study conducted by Devi et al (8)

Induction of labor did not increase the incidence of PPH in gestational hypertension and mild preeclampsia but the overall incidence of PPH found in HYPITAT trial was 10%, which was considerably higher than the 0.4 to1.3% risk of PPH observed in low risk populations.(92)

MATERNAL DEATH

Preeclampsia/eclampsia is one of the 3 leading causes of maternal morbidity and mortality worldwide(93).Around the world each year 10% to 15% of maternal deaths are associated with hypertensive disorders in pregnancy.(94)

The latest report of the American College of Obstetricians and Gynecologists highlights that preeclampsia is responsible for 50,000 to 60,000 death per year and approximately 50 to 100 maternal near-misses for every preeclampsia-related death.(95)Yet another

study by Dadelszen et al estimated that the hypertensive disorders of pregnancy causes 30,000 maternal deaths annually.(96)

HELLP Syndrome is life threatening complication which is associated with a maternal mortality between 1.1 and 3.4%.(97).In a study by Isler et al to determine factors contributing to death among women with HELLP syndrome found that among the events associated with maternal deaths, cerebral hemorrhage was 45%, cardiopulmonary arrest 40%, disseminated intravascular coagulopathy 39%, adult respiratory distress syndrome 28%, renal failure 28%, sepsis 23%, hepatic hemorrhage 20% and hypoxic ischemic encephalopathy 16%. (98)

The incidence of maternal death was 1.1% in both Devi et al and Yücesoy et al's studies showing 2 maternal deaths out of 180 pregnant women with hypertension of which one woman had DIC and the other had thromboembolism(1) , and 3 maternal death among 255 women with pregnancy induced hypertension of which all 3 had HELLP syndrome respectively (6).In a study by Panda et al, maternal mortality in hypertensive mothers was seen in 2.9%,the cause being cerebral hemorrhage and pulmonary edema. (99)

During the past 50 years, there has been a significant reduction in the rates of eclampsia, maternal mortality, and maternal morbidity in the developed countries. But it still remains high in the developing countries due to lack of prenatal care, lack of access to hospital care, lack of resources and inappropriate diagnosis and management of women with preeclampsia and eclampsia. Clear protocols for early detection and management of hypertension in pregnancy at all levels of health care are required for better maternal outcome.(93) The same was described by Berhan and Endeshaw that the the majority of

maternal deaths were linked to delay in providing obstetric care , delay in arrival, or delay in initiation of appropriate treatment and also in that study, maternal death was reported to be 5% and the majority died after they developed eclampsia.(100) The WHO populational study also showed a very high mortality rate in women with eclampsia (3.66%).(101)

The UK 'Confidential Enquiries into Maternal Deaths' has identified that the most serious fault in the care of women who died due to stroke was the failure to recognize the severity and to treat the severe hypertension (particularly systolic) of preeclampsia.(99)

2. PERINATAL COMPLICATIONS

FETAL GROWTH RESTICTION

Pregnancy induced hypertension is the single most common etiological factor for fetal intrauterine growth restriction(102). Increased blood pressure leads to decreasing uteroplacental blood flow, thus causing reduced oxygen flow to the fetus causing growth restriction. The prevalence ranged from 15-30% in various studies in India. (1)(52)(60) . Similar rates (25%) have been reported in other countries as well.(7)

Early onset preeclampsia had high association with fetal growth restriction. The typical features were an incomplete trophoblast invasion, an inadequate transformation of spiral arteries, followed by respective changes in the blood flow of the uterine arteries, alterations of the umbilical blood flow and restrictions of fetal growth.(103)

The FGR incidence was 22.4% in women with severe preeclampsia and 18.6% in women with chronic hypertension with superimposed preeclampsia in a study by Zhu et al. It also showed that in the hypertensive population, the risk of FGR in women with a previous FGR history was increased by four-fold. (104)

According to Weiler et al, the presence of FGR was not associated with a more severe maternal preeclamptic presentation , however higher neonatal mortality was seen.(105)But in a study by Zhu et al, the incidence of HELLP syndrome in hypertensive pregnant women doubled when complicated with FGR. (104)

PRETERM

Iatrogenic preterm delivery for maternal sake is a major risk for prematurity in pregnancies complicated by hypertensive disorders. The incidence of preterm birth was high ranging from 34 to 59.6% (106–108).Some studies showed lower prevalence of 28.85% as in Yadav et al study (109)and 10.9% according to Chaim et al (110) . Kolluru et al study also showed that second most common fetal complication after IUGR was preterm accounting to 31.6%.(52)

Women with chronic hypertension progressing to preeclampsia were at 43-fold higher risk of a medically indicated preterm birth less than 32 weeks compared with women without chronic hypertension according to Premkumar et al.(111)Also in that study ,the incidence of preterm delivery in chronic hypertension was 26.2% and in gestational hypertension was 21.6%.Women with chronic hypertension or gestational hypertension

had a higher risk of medically indicated and spontaneous preterm birth , both less than 32 and 32 to 36 weeks, when compared with non hypertensive women.(111)

Rasmussen et al in their study suggested that preterm birth and preeclampsia share pathophysiologic mechanisms and these mechanisms may cause preterm birth in one pregnancy and preeclampsia in a subsequent pregnancy in the same woman.(112) In a study by Lakshmikanth and Sudharshana, the incidence of prematurity was 50% when diastolic blood pressure was more than 110mmHg.(113)

RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome in the newborn (RDS) is a disease caused by the absence or inadequate production of pulmonary surfactant and the related underdevelopment of the lungs.(114)

Preeclampsia is a complication characterized by an anti-angiogenic environment. This can affect fetal pulmonary vascular and alveolar development and can be associated with increased risk of severe RDS (115). In a study by Soomro et al, 4.4% of babies born to hypertensive mothers had RDS, 60% belonging to preeclampsia group.(60) Contrasting to the above finding, in a study by Yoon et al the incidence of infant RDS was 15.2% in the hypertensive pregnant women group which was significantly lower than the 29.9% in the non-hypertensive pregnant women group concluding that chronic stress accelerates fetal lung maturation .(116).The same result was found by Agashe et al that PIH was associated with statistically significant decrease in incidence of RDS suggesting

acceleration of pulmonary maturity. Pregnancies complicated by hypertension were associated with raised maternal ACTH levels and reduced plasma cortisol levels. The maternal adrenal gland in PIH may be relatively unresponsive to ACTH stimulation so excess ACTH crosses the placenta and induces maturity of surfactant by causing release of glucocorticoids in fetus.(117)

The risk for neonatal respiratory disorders increased with severity of maternal hypertension and the observed associations were present in both full-term and preterm birth according to a study by Tian et al.(118)

Chronic hypertension was strongly associated with early gestation RDS(<32 weeks) whereas eclampsia was strongly associated with late gestation RDS (≥39 weeks).(119)

MECONIUM ASPIRATION SYNDROME

It is defined as respiratory distress in the newborn due to the presence of meconium in the trachea.(120) It can also be defined respiratory distress in an infant born through meconium-stained amniotic fluid (MSAF) whose symptoms cannot be otherwise explained.(121) About 2 to 9% of infants born through MSAF develop meconium aspiration syndrome.(122)

Pregnancy induced hypertension can cause placental dysfunction and lead to fetal hypoxia, which may lead to the development of meconium aspiration syndrome.(123) Phirke et al observed that 14% of babies born to hypertensive mothers had meconium aspiration syndrome, constituting to third most common risk factor for MAS (124) .The

incidence of MAS in hypertensive mothers was 5.4% in a study by Swetha Anand et al (125) and 6.22% as observed in a study by Obsa et al. (126)

The presence of meconium stained amniotic fluid at delivery is a potential sign of fetal compromise.(127) Meconium passage may be just a physiological consequence of increased levels of intestinal hormone, motilin (124) or may be associated with several maternal and neonatal risk factors like hypoxia, placental insufficiency, preeclampsia, maternal hypertension, maternal diabetes mellitus, post term pregnancy, oligohydramnios and intrauterine growth restriction.(127).Hence passage of meconium can be considered physiological, exhibiting sign of fetal maturity on one hand whereas on the other hand, a sign of fetal distress and response to hypoxic insult.(128) In a study by Patel et al,17% babies born to hypertensive mothers had meconium stained amniotic fluid.(129) The same was shown in a study by Mundhra et al that pregnancies complicated with PIH had statistically significant higher rates of meconium staining than those with healthy pregnancies (16.97% versus 7.89%, $p < 0.05$).(130) Hence it is strongly recommended that hypertensive mothers have early and appropriate care along with constant monitoring.

LOW BIRTH WEIGHT

According to the World Health Organization (WHO), Low birth weight (LBW) is defined as a birth weight of less than 2500 grams irrespective of the gestational age.(131)

Maternal hypertension is an important risk factor for low birth weight.(132) Women who had PIH were nearly nine times at increased risk of LBW according to Zenebe et al. This might be due to hypertension resulting in decreased blood flow through the spiral arterioles and decreased delivery of oxygen and nutrients to the placenta and fetus and also might be associated with placental infarction. So the odds of LBW among women who had PIH were higher when compared to normotensive women. This finding is in line with WHO secondary analysis survey which was conducted in low and middle income countries, which confirmed that the risk of acquiring LBW among women with PIH was double (133).

In a study by Xiong et al, for women delivering before 37 weeks of gestation, birth weights remained significantly lower among babies born to women with gestational hypertension than among babies born to women with normal blood pressure ($p < 0.01$). But for women delivering at ≥37 weeks of gestation, there was no statistically significant difference in mean birth weights between women with gestational hypertension and normal blood pressure.(134) The same finding was found among women with preeclampsia. A possible explanation for these findings is that preeclampsia requiring delivery prior to ≤37 weeks of gestation are more likely to be severe and more likely to have a detrimental effect on fetal growth.

Preeclampsia was more prone for low birth weight babies compared to gestational hypertension. The incidences of LBW were 3.58%and 6.02%for women with gestational hypertension and preeclampsia respectively, relative to 2.1% for women with normal

blood pressure group according to Liu et al. (135) In a study by Hossain et al, 31% of low birth weight was in preeclampsia,49% in severe preeclampsia and 52% in eclampsia.(136)

INTRA UTERINE DEATH AND STILLBIRTH

Women with hypertensive disease in pregnancy are at significantly higher risk of having pregnancies complicated by stillbirth in comparison with women with normotensive pregnancies.(137) PIH is a major risk factor for stillbirth, increasing the odds by 1.2 to 4 fold.(138) Hypertensive disorders contribute to 9.2% of stillbirths according to Basso et al.(139)In a study to find the causes for intrauterine fetal death by Deshpande et al, PIH constituted 22.5% of intrauterine fetal death(IUFD)(140) and it was 24.9% in a study by Kumar et al forming the most common cause for stillbirth.(141) Chronic hypertension increases stillbirth risk by almost three-times.(142). Soomro et al study showed 11 intrauterine death out of 112 women with hypertensive disorders of pregnancy, of which maximum (45.5%)was in eclampsia group. (60)

Fetal growth restriction and placental abnormalities are the most common findings in stillbirth.(143) Placental insufficiency is often implicated in stillbirth, especially in the setting of preeclampsia. Parenchymal infarction was the one lesion associated with stillbirths in women with preeclampsia or gestational hypertension, but only in the preterm stratum.(138)As already said ,hypertension can lead to placental abruption which also results in 10 to 20% of all stillbirths and larger the area of placental separation, the greater is the risk of fetal demise.(11)

The risk of stillbirth was high among multiparas with PIH than primigravidas.(144) In a study by Hossain et al, one of the main fetal complication in pregnancy complicated by hypertension was still birth of which 14% was in non severe preeclampsia, 18% in severe preeclampsia and 15% in eclampsia .(136)

NEONATAL DEATH

The prevalence of perinatal mortality in women with hypertensive disorder of pregnancy was 14.9% in a study by Panda et al and was significantly higher in women with eclampsia and severe preeclampsia (p-value <0.0001) and more so in eclampsia than in severe preeclampsia (p-value <0.0001).(99)

In a study by Rajamma and Sridevi among women with hypertensive disorder complicating pregnancy, early neonatal death accounted for 9.8%.Also in this study, maximum perinatal mortality was found when the BP was above 160/110 mmHg and proteinuria 3+ and above. (145) The same was found in a study by Endeshaw G et al where a statistically significant association of perinatal mortality with the highest systolic BP ≥160 mmHg and diastolic BP ≥110 mmHg was present.(146)

The probable reasons for high incidence of neonatal death in hypertensive disorders of pregnancy are prematurity, intrauterine fetal restriction and low birth weight. It was observed that nearly three-fourths of the perinatal deaths (71%) in women with antepartum onset of hypertensive disorder of pregnancy were either preterm or very preterm at birth.(146) The incidence of neonatal death in a study by Lakshmikanth and

Sudharshana was 17.1% of which incidence of neonatal deaths was high among preterm infants (46.9%) as compared to term infants (3.7%). Also incidence was highest (76.9%) between gestational age of 28-30 weeks and thus the leading cause of neonatal death was prematurity(37%) followed by severe birth asphyxia and septicemia (18.5% each).(113)

On the other hand, significantly increased odds of perinatal mortality was observed among women with eclampsia. This is most probably because of the severe nature of the eclampsia disease, which usually complicates by severe intrauterine asphyxia, severe placental abruption, and neonatal sepsis. (146)In the study by Lakshmikath et al, 40.7% neonatal death was in eclampsia.(113)

The major reason for high perinatal loss may be due to delayed referral and lack of antenatal care and high incidence of preterm births. Hence early detection of failing placental function, timely delivery, judicious use of drugs in the mother which affects the fetus adversely and adequate neonatal intensive care facilities is necessary to improve neonatal outcome.(113)

MATERIALS AND METHODS

Study design:

Prospective observational study

Setting and location:

Women with hypertensive disorders in pregnancy were recruited from obstetrics ward and labour room in the Department of Obstetrics and Gynecology in Christian Medical College, Vellore, Tamil Nadu

Recruitment:

The women who were diagnosed with atleast one pregnancy related hypertensive disorder(Gestational hypertension, preeclampsia, eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension) ,who met the inclusion criteria were recruited from obstetrics ward and labour room, irrespective of age, parity and gestational age, after taking informed written consent. They were observed for development of any complication during their hospital stay (before, during and after delivery or expulsion).The maternal outcome and perinatal outcome were noted.

Study duration:

The study was carried out from April 2020 to October 2021 after approval from Institutional Review Board (IRB Min .no. 12609 dated 05/02/2020)

Sample size:

A sample of size 400 required to obtain a 95 CI of 5% around an expected prevalence of normal vaginal delivery of 50%.(8)

Formula:

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

where n is the required sample size; Z1-α/2 is the percentage point of standard normal distribution corresponding to the chosen level of confidence; p is the expected prevalence of the outcome of interest; d is the desired level of precision.

Quantitative variables assessed:

Age of mother, gestational age, postpartum hemorrhage, preterm, low birth weight

Statistical methods:

Patient characteristics was summarised with counts and percentages for categorical variables. Quantitative variables were summarised as mean and standard deviation or median and range (interquartile range) for normally and non-normally distributed variables, respectively. Chi-square test was used to test association between qualitative variables and two sample t-test was used to compare the means between two groups. All statistical analysis was done using Stata software with Stata IC 16 version.

Inclusion criteria:

Women with singleton pregnancy and hypertensive disorder of pregnancy were included in the study after informed written consent

Exclusion criteria:

Women who don't consent for the study and multiple pregnancy were excluded

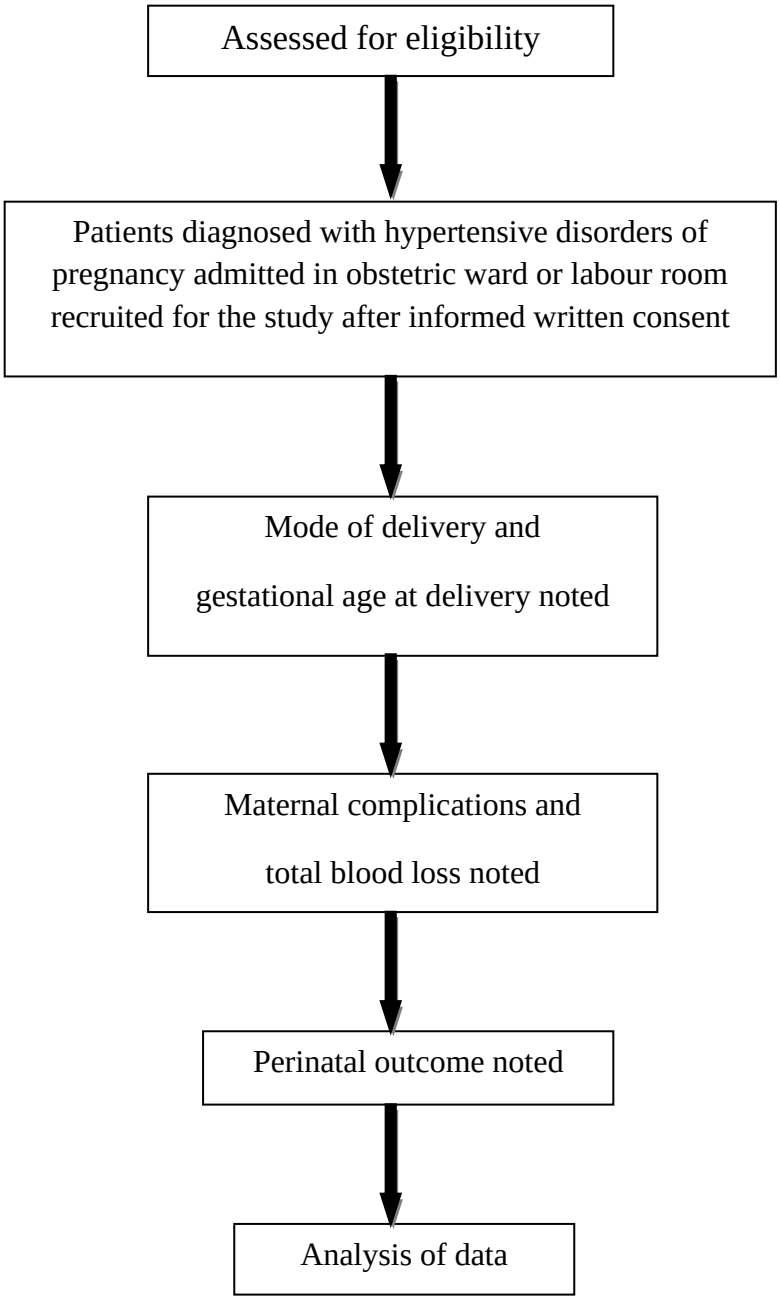
Methodology:

Booked pregnant women diagnosed with hypertensive disorders of pregnancy who got admitted in obstetric wards or in labor room in Christian Medical College, Vellore were included in the study after getting informed written consent. They were observed for development of any complication during their hospital stay (before, during and after delivery or expulsion).

Details like gestational age at diagnosis of hypertension and type of hypertension, presence of risk factors for hypertension, need for antihypertensives, mode of delivery, gestational age at delivery, blood loss, maternal complications and perinatal outcomes including birth weight, Apgar scores, perinatal complications were noted.

Data entry was done using Epi-data 3.1version. Data analysis was done using Stata IC 16 version.

PROPOSED ALGORITHM



RESULTS

Booked pregnant women diagnosed with hypertensive disorders of pregnancy who got admitted in obstetric wards or in labor room in Christian Medical College, Vellore were recruited in the study after getting informed written consent. We observed 400 women with singleton pregnancy and hypertensive disorder.

Age and hypertensive disorder of pregnancy:

Women between the age of 19 and 35 years of age had the maximum incidence of hypertensive disorder of pregnancy accounting to 93%(n=372).

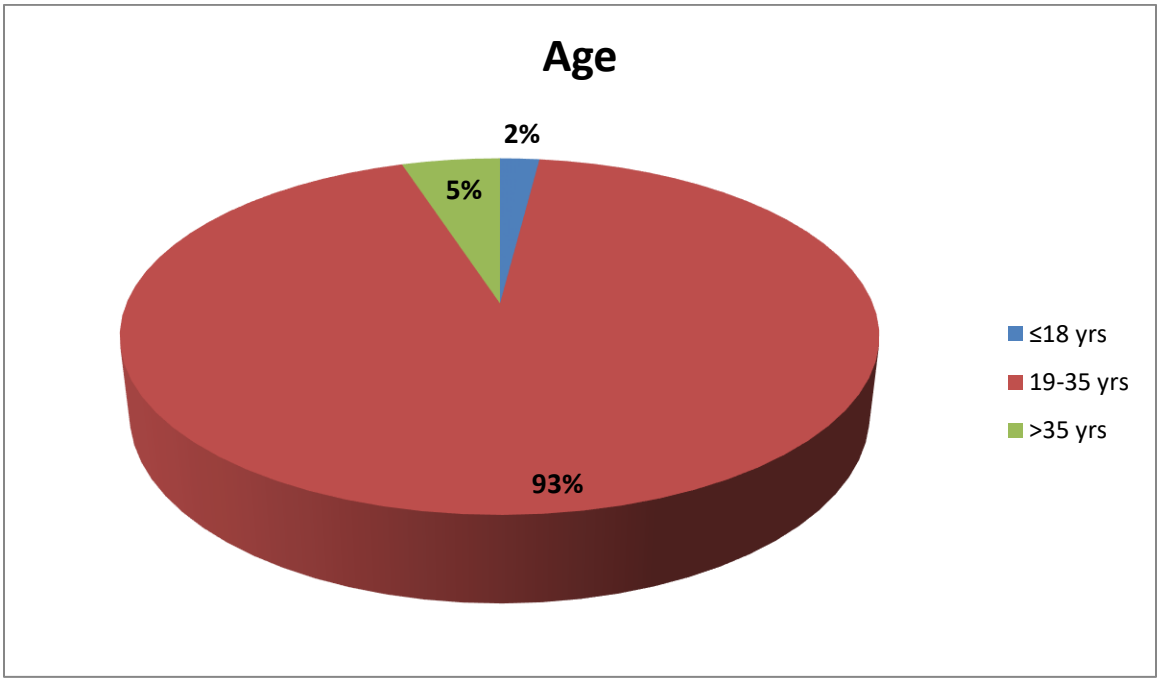


Fig. 7 Age and hypertensive disorder of pregnancy

Parity and hypertensive disorder of pregnancy:

The incidence of hypertensive disorder was more in primigravida when compared to multigravida. Out of 400 pregnant women with hypertensive disorder, we found that 257(64.2%) women were primigravida and 143 (35.7%) were multigravida.

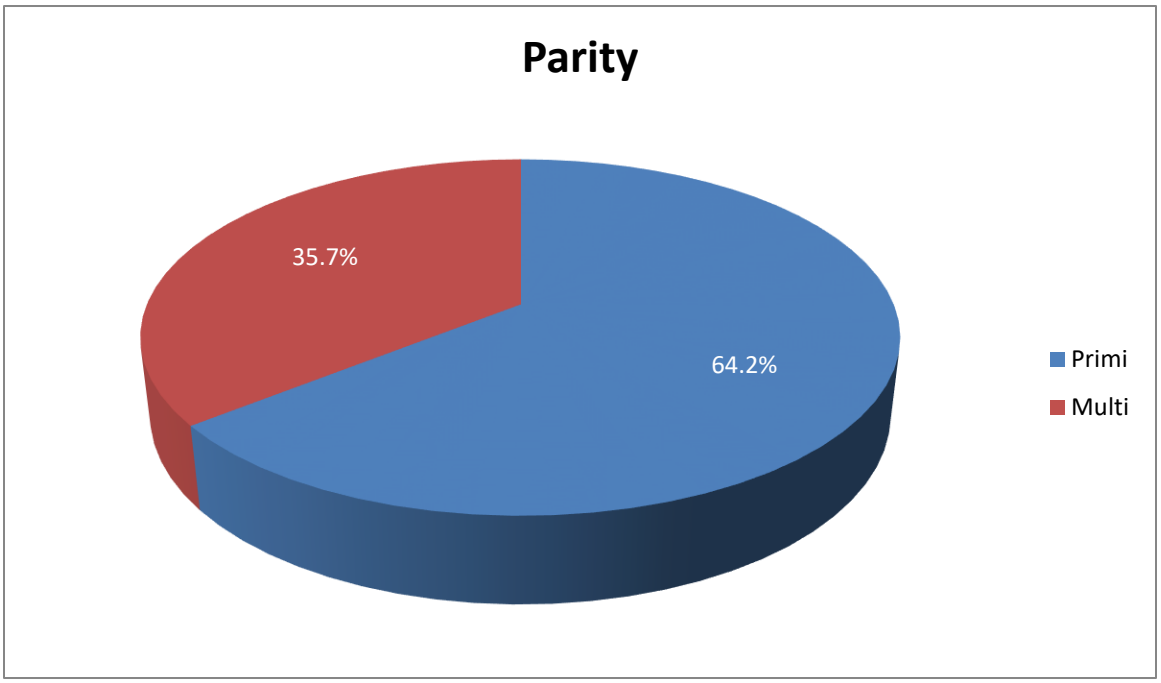


Fig.8 Parity and hypertensive disorder of pregnancy

Medical co-morbidities:

The most common medical co-morbidity which was found in hypertensive pregnant women was diabetes mellitus followed by anemia and hypothyroidism. 33% (n=132) out of 400 pregnant women with hypertension had diabetes of which 81%(n=107) had gestational diabetes and 18.9%(n=25) had pregestational diabetes.

16.2% (n=65) of them had anemia complicating pregnancy and 12.2%(n=49) had hypothyroidism. Bronchial asthma was found in 2.2% (n=9) and seizure disorder was seen in 1.5 % (n=6). Renal disorder namely nephrotic syndrome and chronic kidney disease was seen in 0.75%(n=3).

2(0.5%) out of 400 women had APLA and the same was found for SLE(0.5%).Other autoimmune diseases like autoimmune hemolytic anemia, Takayasu arteritis, thrombotic thrombocytopenic purpura was found in 0.75%.

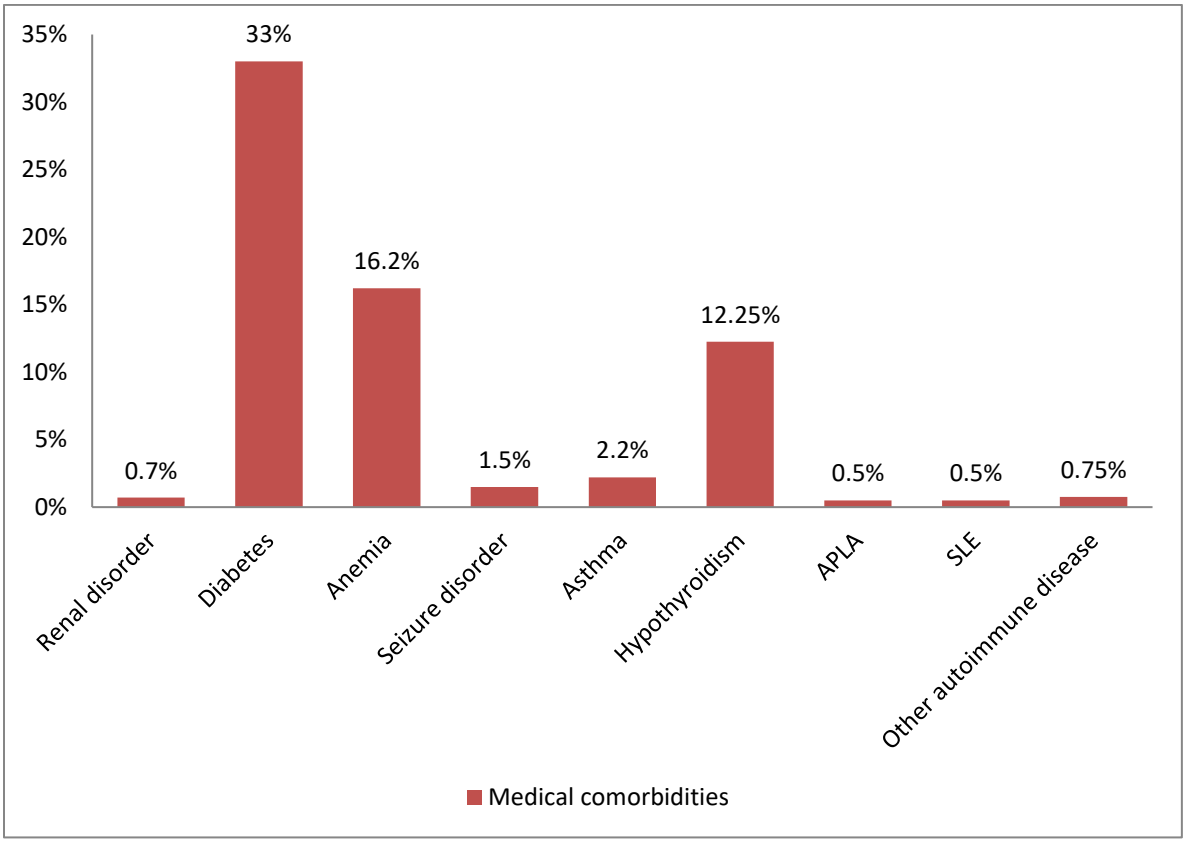


Fig.9 Medical co-morbidities

Risk Factors:

Out of 400 women, 129 (32.2%) of them had family history of hypertension and 17.2%(n=69) were obese.

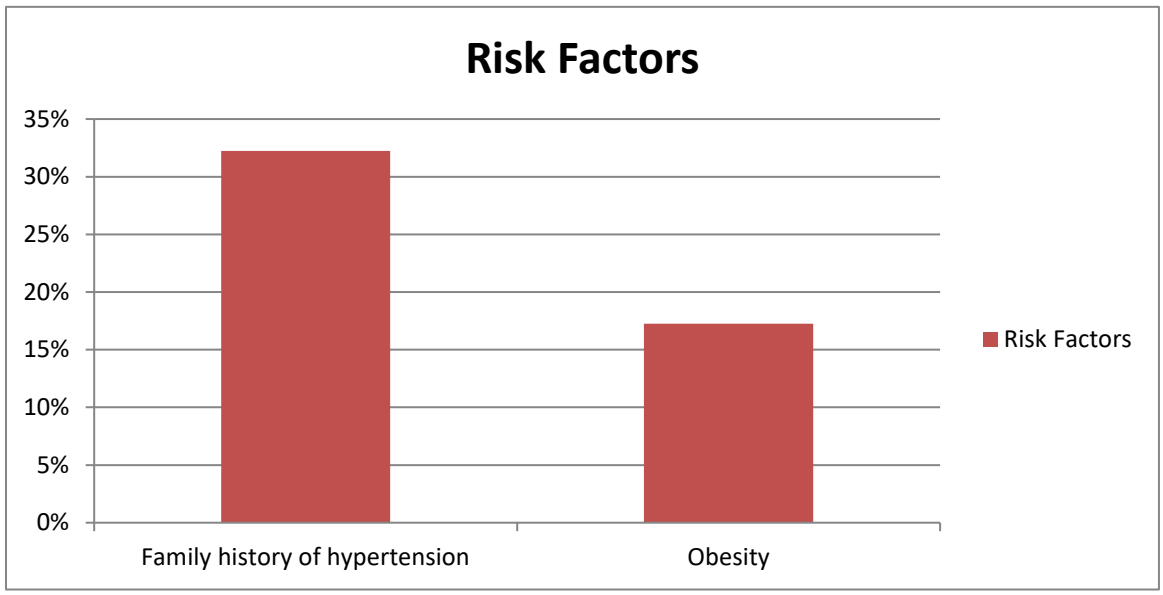


Fig.10 Risk Factors

Among 143 multiparous women, 31% (n=45) had history of hypertension in their previous pregnancy.

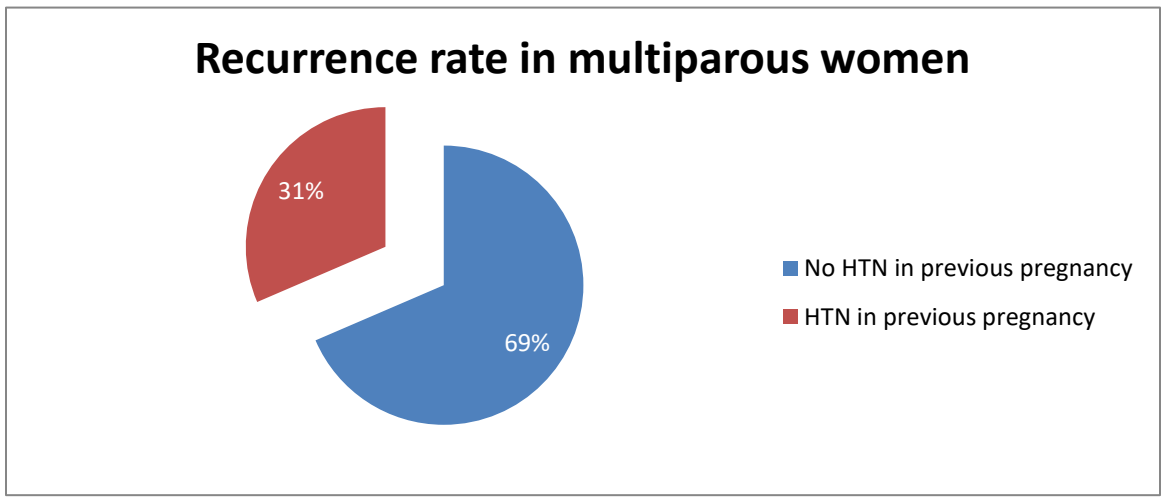


Fig. 11 Recurrence rate in multiparous women

Antihypertensive agent:

78.75% (n=315) of women among 400 hypertensive pregnant women, required antihypertensive agents to control the blood pressure in their antenatal period.

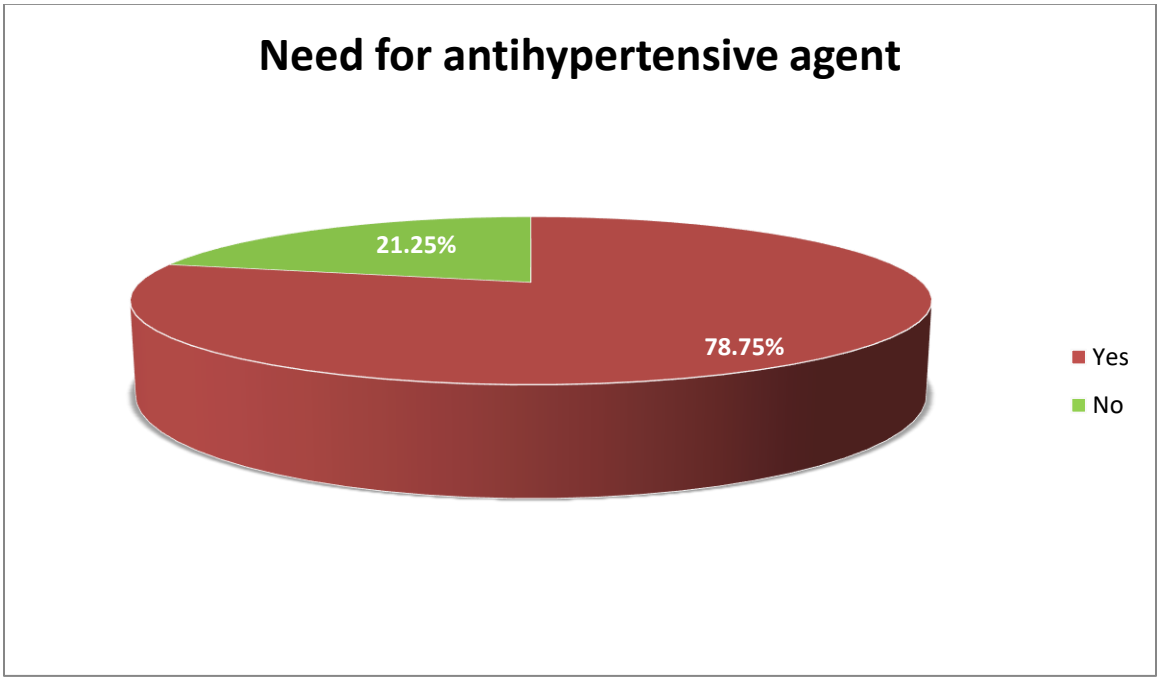


Fig.12 Need for antihypertensive agent

Among the 315 women who required antihypertensives antenatally, the predominant antihypertensive agent used was beta blocker (Labetalol) accounting to 74.2%(n=234).Calcium channel inhibitors (Nifedipine) was received by 4.4 %(n=14) whereas 21.2%(n=69) required two antihypertensive agents, both labetalol and nifedipine to control their blood pressure.

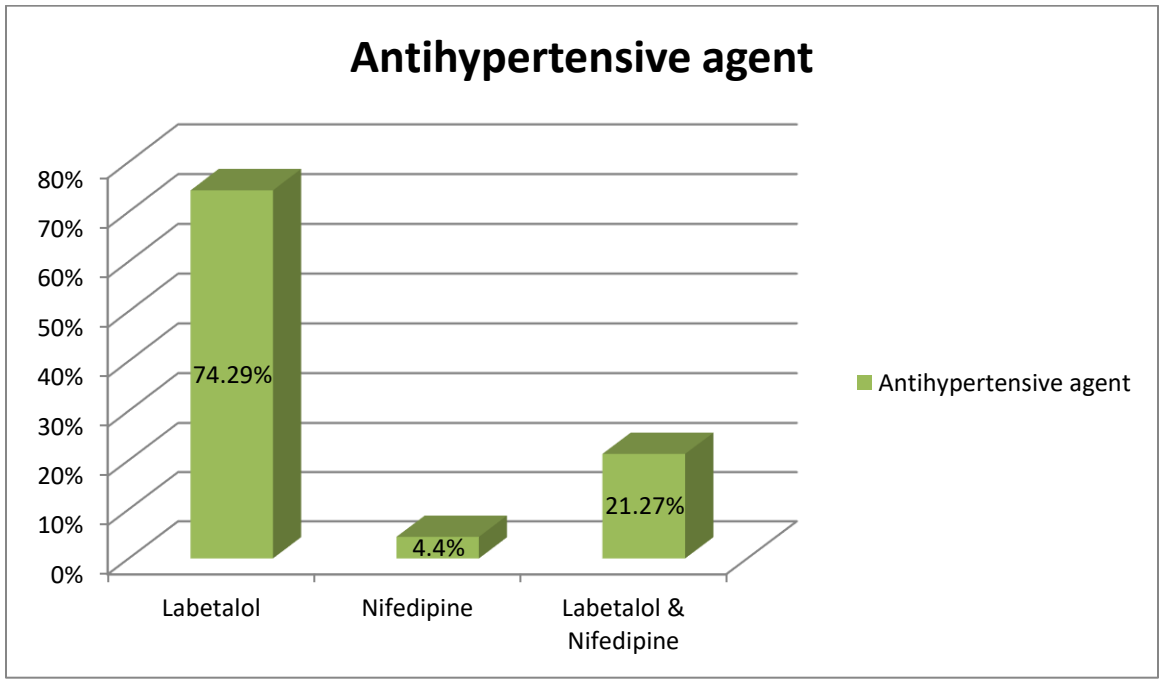


Fig.13 Type of antihypertensive agent

Type of hypertensive disorder:

We found that 42%(n=168) had preeclampsia among which majority of 167 women had severe preeclampsia and only one woman had non severe preeclampsia. This was followed by gestational hypertension which was found in 39 %(n=156) and chronic hypertension which was seen in 10% (n=40). The incidence of both eclampsia (antepartum and intrapartum) and preeclampsia superimposed on chronic hypertension was 4.5%(n=18) independently.

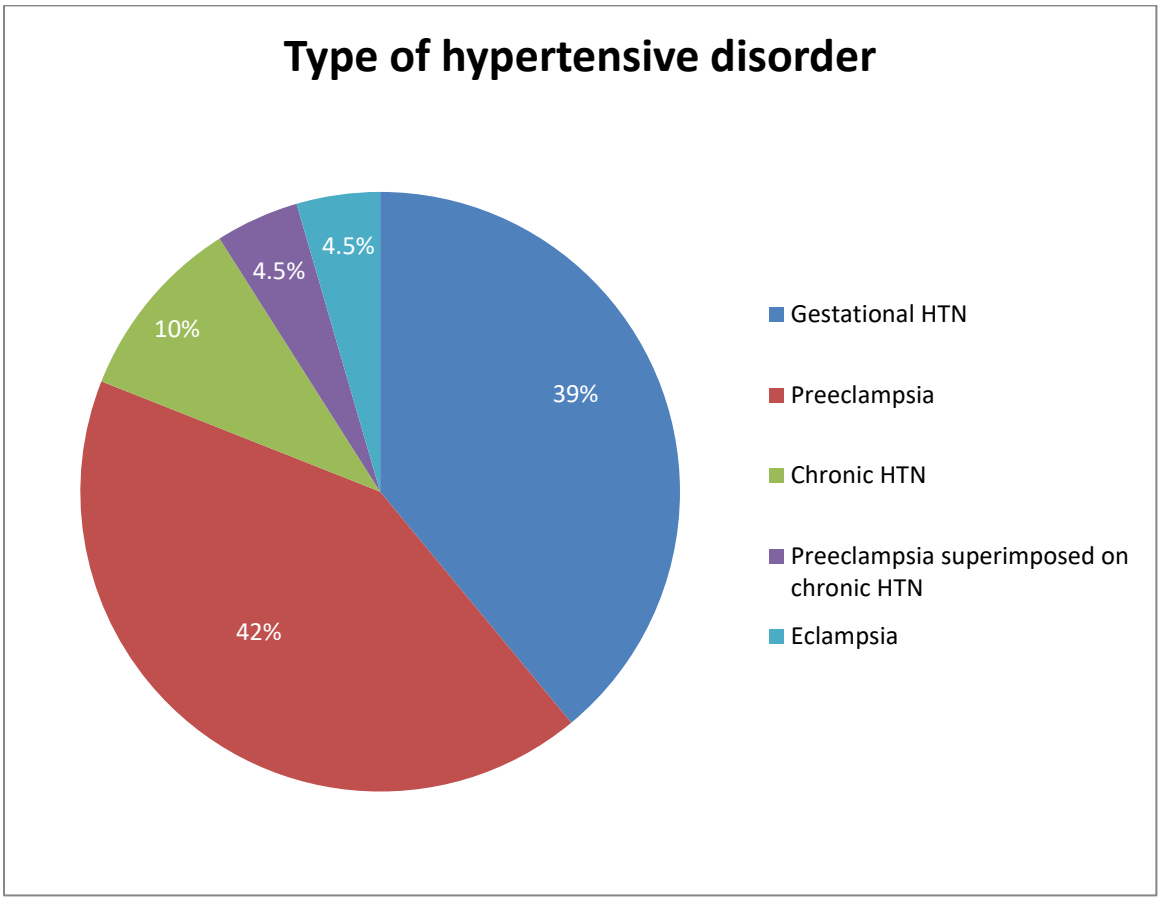


Fig.14 Type of hypertensive disorder

Gestational age at delivery:

The majority of 55.89% women had delivery at term followed by 22.06 % of women who had delivery between 34+1 week to 37 weeks of gestation and 14.4 % of women who had delivery between 28+1 week to 34 weeks. 4.7 % had delivery postdates and 3.2% women had extreme preterm delivery (less than 28 weeks of gestation).

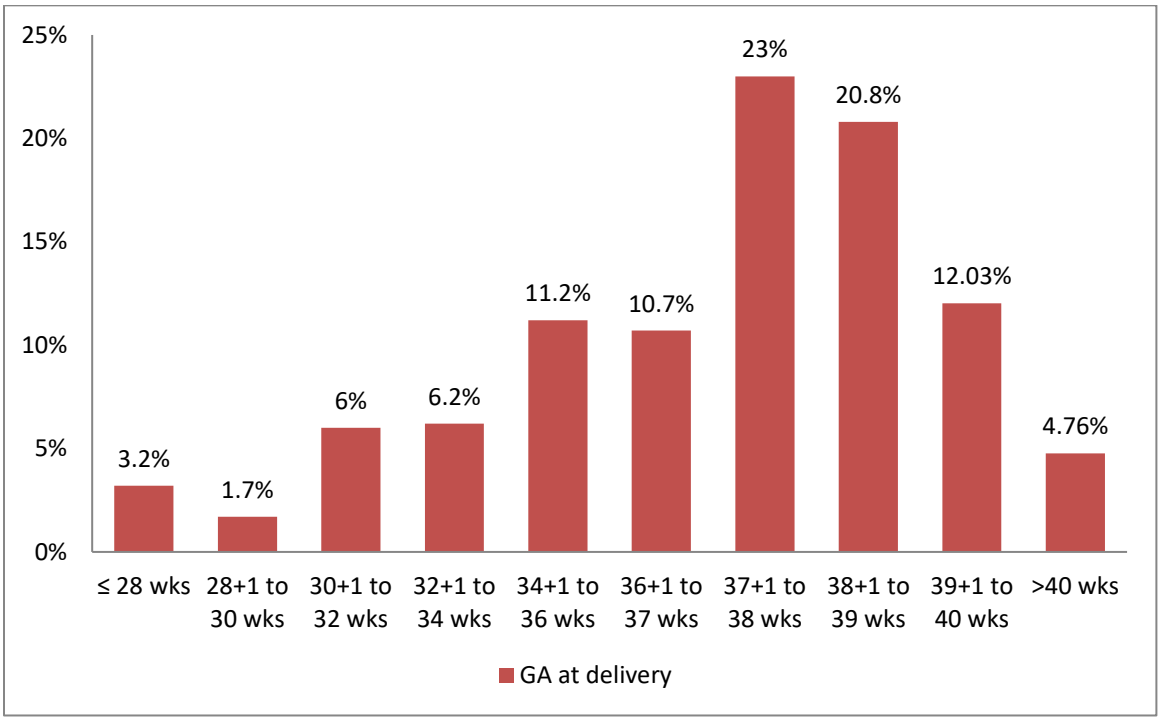


Fig. 15 Gestational age at delivery

Onset of labour:

The induction rate was high which amounted to 71.75%(n=287). 7.5 % (n=30) of women had spontaneous onset of labour in our study. Reminder 20.75% (n=83) of women were not in labour but required delivery due to obstetric or maternal indications.

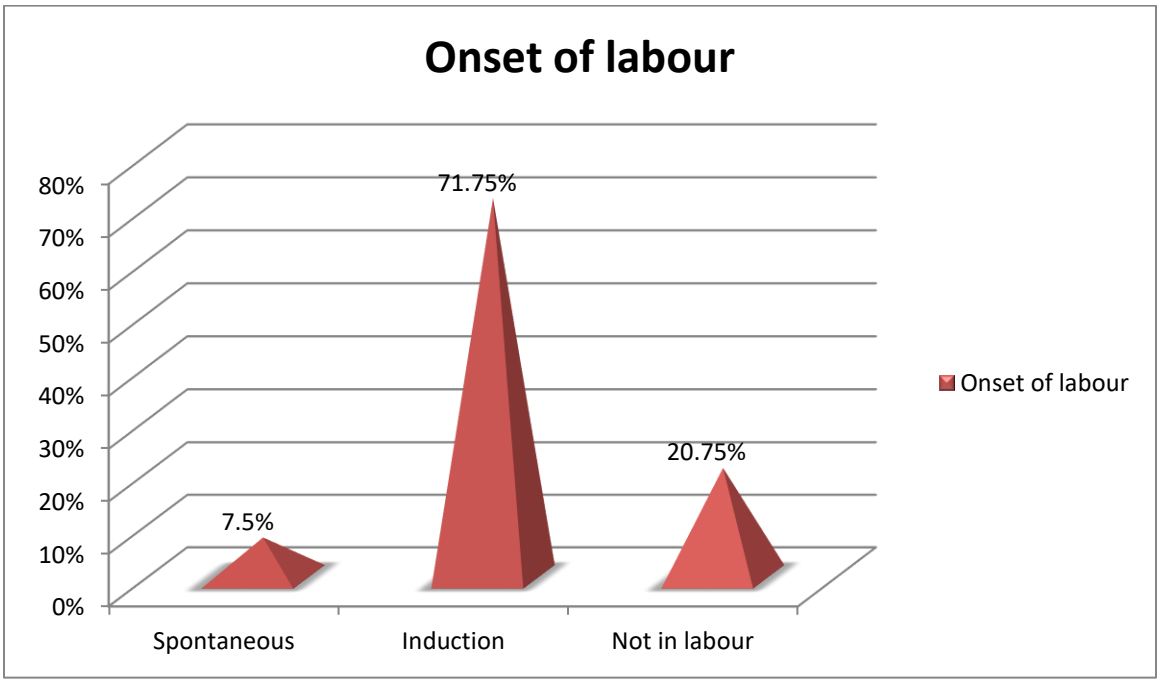


Fig. 16 Onset of labour

Indication for induction:

Among 287 women who underwent induction, the percentage of women who was induced for indication related to hypertension was extremely high. 83.62% (n=240) women underwent induction due to hypertension and 16.38 % (n=47) for other indication.

Premature rupture of membranes was the commonest indication for induction among the 47 women who had inductions not related to hypertension amounting to 40.43%, followed by diabetes contributing to 12.7 %.

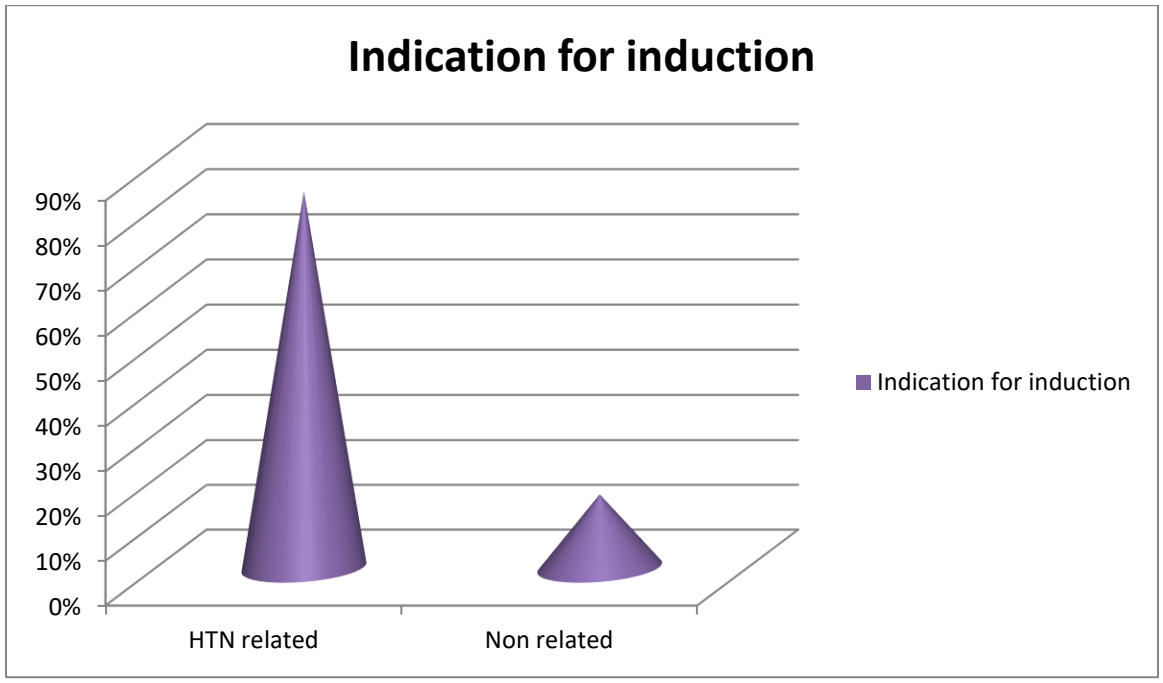


Fig.17 Indication for induction

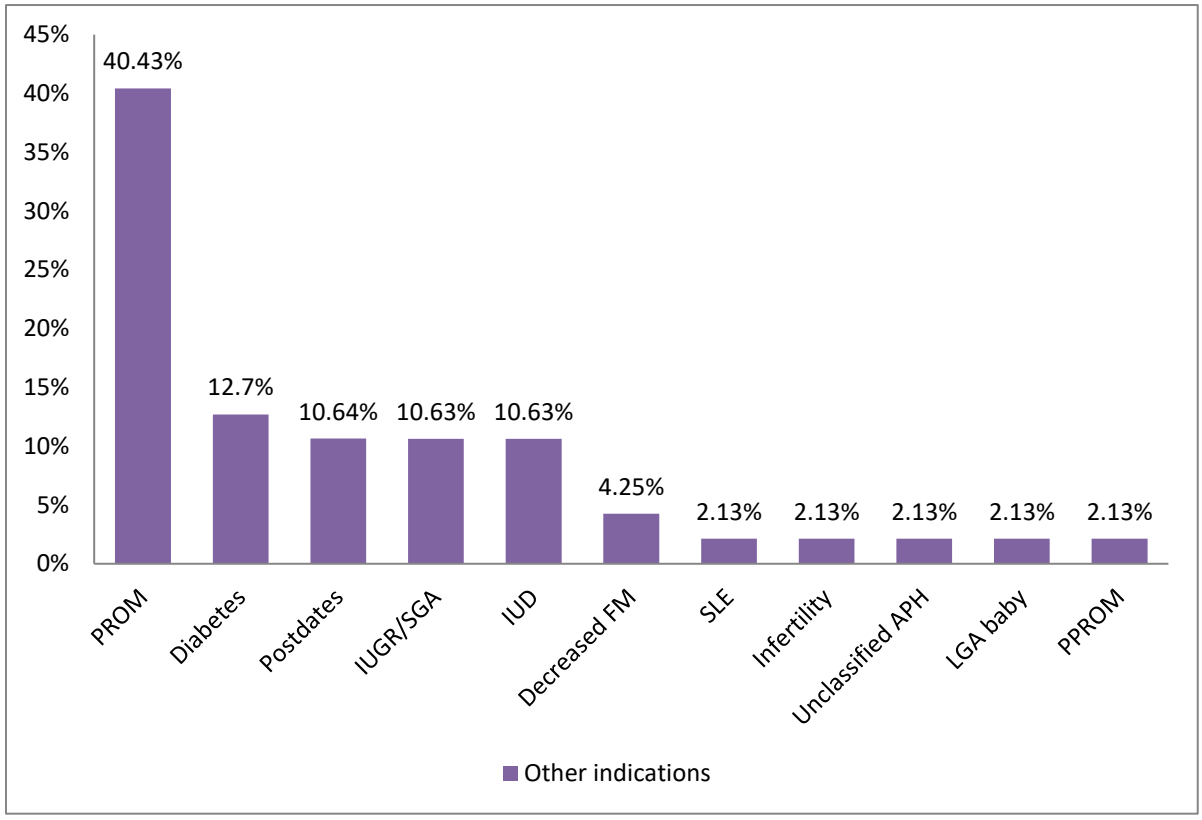


Fig.18 Other indication for induction

Mode of induction:

49.48% of women were induced only with PGE 1 and 38.68% required both Foleys and PGE 1 according to Bishops's score.10.45% of women were augmented with oxytocin alone without any cervical ripening agents and 1.39% were induced only with Foley's.

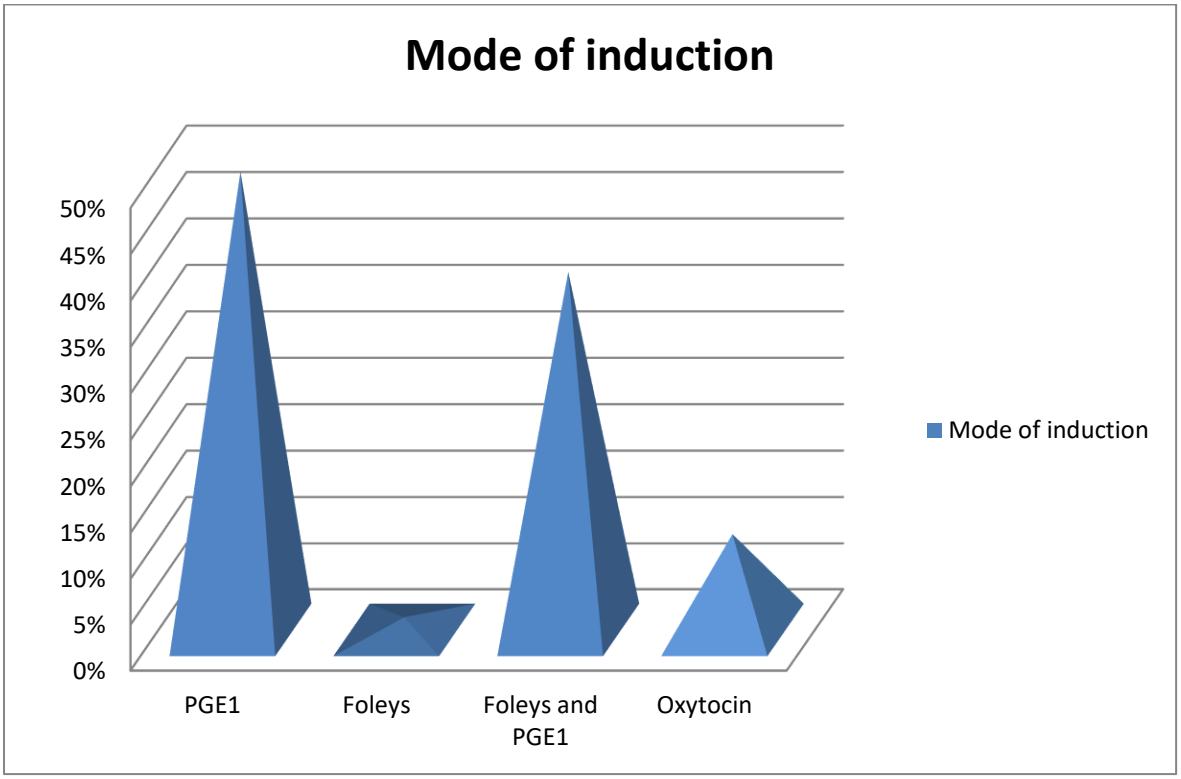


Fig.19 Mode of induction

Mode of delivery:

The LSCS rate was the highest in our study accounting to 51.75%(n=207) of which 98% was emergency LSCS and 1.93% was elective. 32.25%(n=129) of women delivered by normal vaginal delivery and 13.75 %(n=55) had forceps delivery followed by 2.26% (n=9) of women who had vacuum delivery. The main indication for instrumental delivery was non reassuring fetal status which accounted to 78% followed by 12.5% to cut short second stage of labour and 9.3% for prolonged second stage .

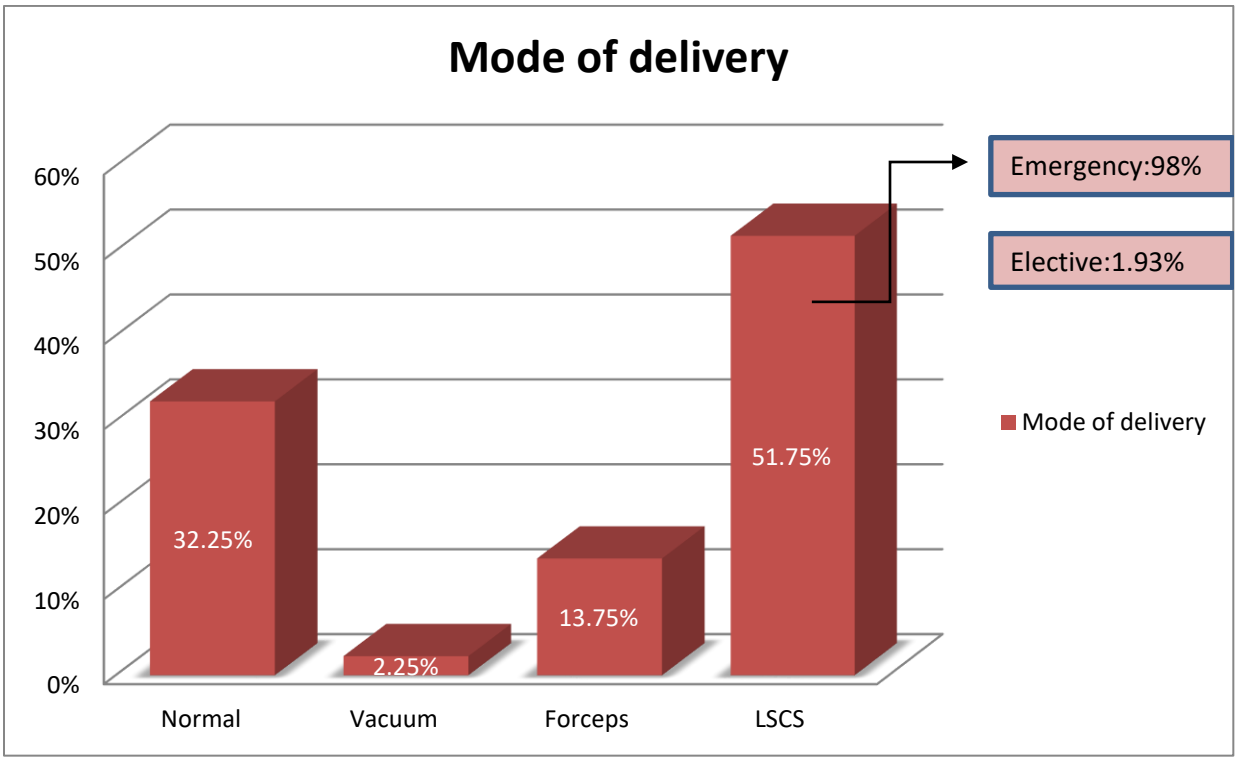


Fig.20 Mode of delivery

Indication for LSCS:

Among 207 women who had cesarean section, 40 women had more than one indication. The commonest indication for LSCS was non reassuring fetal status which contributed to 37.19% (n=77), followed by deteriorating maternal condition [22.22%(n=46)] and failed induction [21.74% (n=45)].

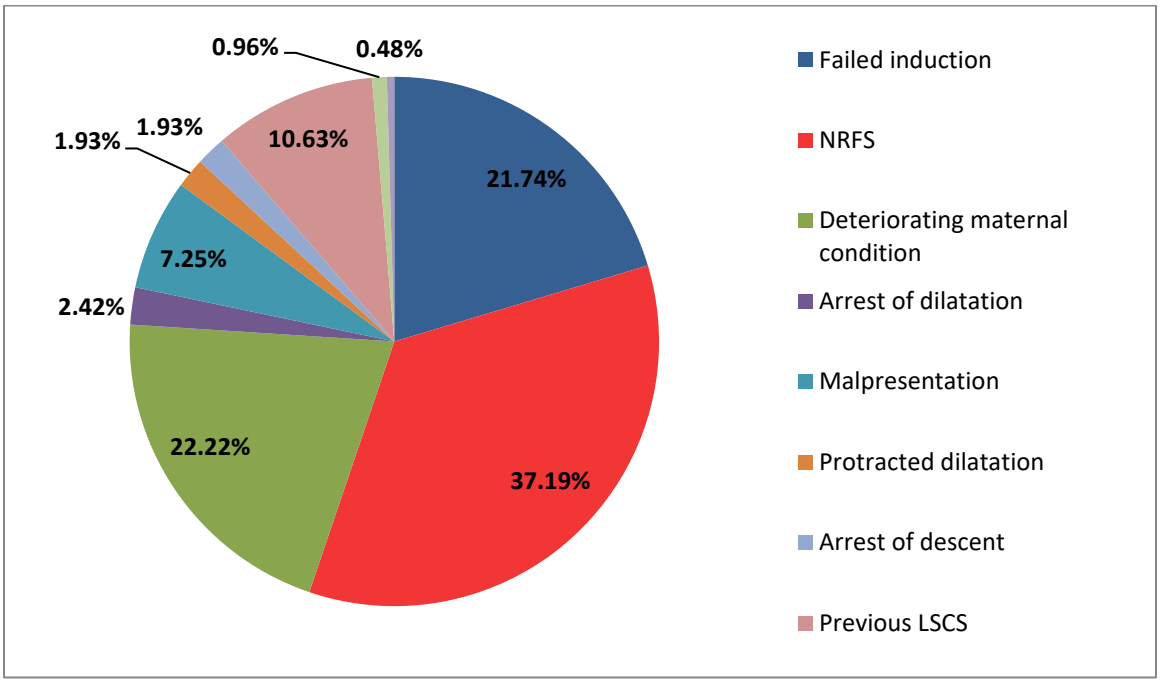


Fig.21 Indication for LSCS

Maternal complication:

Postpartum hemorrhage was seen in 10.75% (n=43) of hypertensive women making it the most common complication .

5%(n=20) of women had eclampsia of which 70% (n=14) had antepartum eclampsia, 10 %(n=2) had intrapartum eclampsia and 10%(n=2) had postpartum eclampsia. The 2 women who had postpartum eclampsia had severe preeclampsia during their antenatal period.

We found placental abruption in 3.75%(n=15) of hypertensive women. Partial HELLP and HELLP syndrome accounted for 3.25 %(n=13) and 1.5% (n=6)respectively. Pulmonary edema and acute renal failure accounted for 1 % (n=4) each and posterior reversible encephalopathy syndrome was seen in 3 women (0.75%).Also one woman had disseminated intravascular coagulation accounting to 0.25%.

We did not find acute respiratory distress syndrome, cerebrovascular accidents or any maternal death in our study.

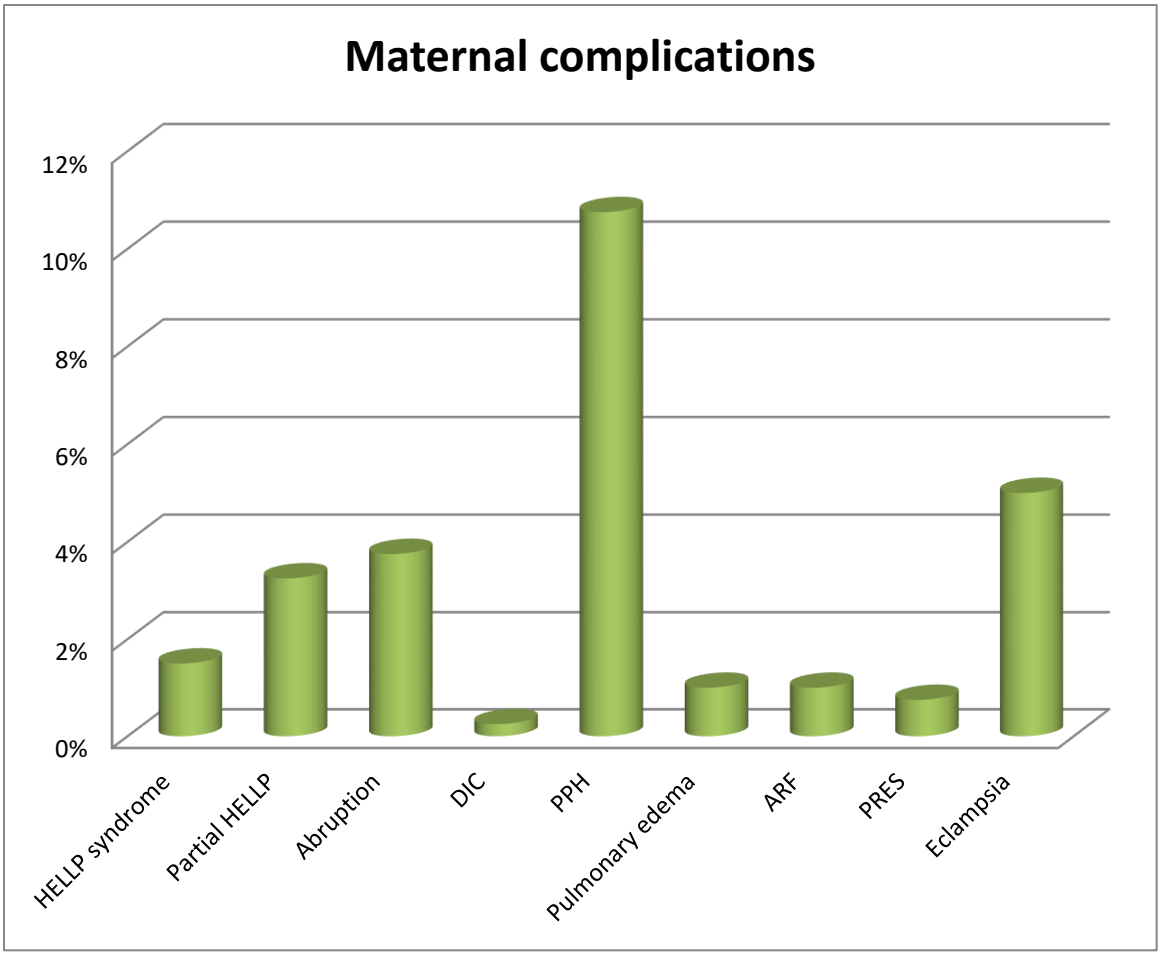


Fig.22 Maternal complications

Total blood loss:

58.75% (n=235) of women had blood loss less than 500ml but 38.25% (n=153) of women had blood loss between 500ml and 1000ml. 12 women (3%) had blood loss more than 1000ml.

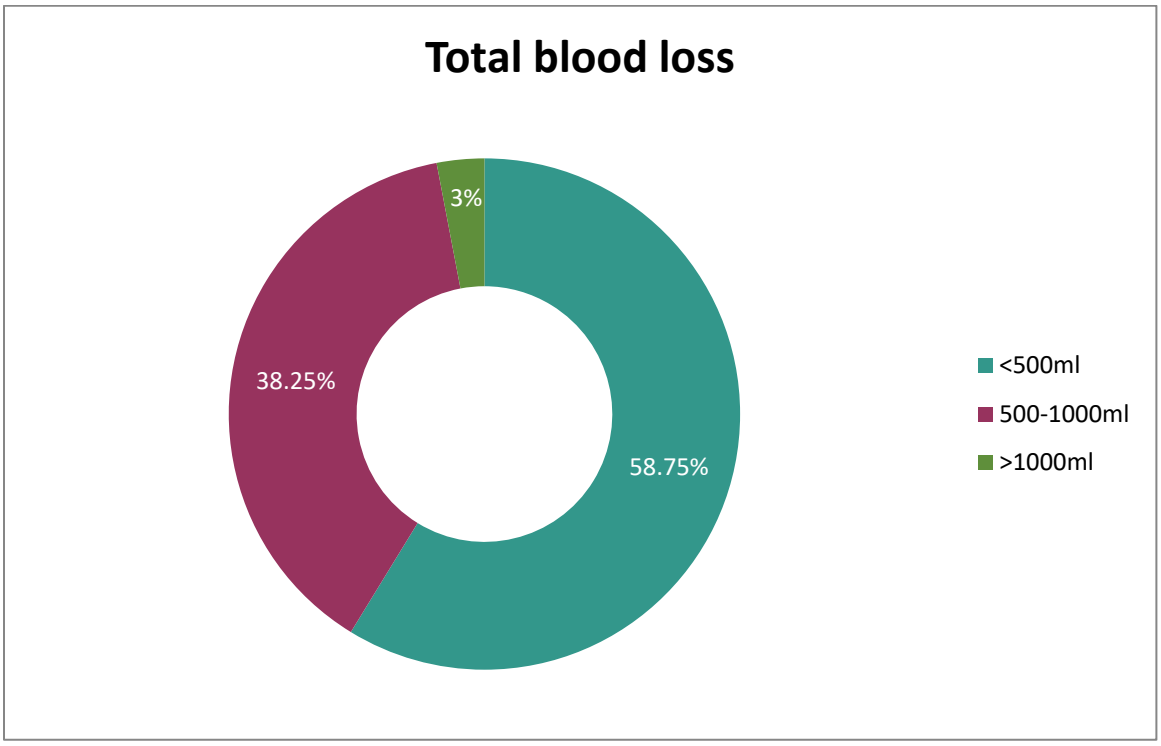


Fig.23 Total blood loss

Postnatal antihypertensives:

Requirement of postnatal antihypertensives was found in 71% (n=284) of women. Of the 284 women, 78.52%(n=223) of women required only one antihypertensive for optimization of blood pressure postnatally and 16.5%(n=47) of women needed atleast two antihypertensive . ≥ 3 antihypertenives were required in 4.9%(n=14) of women in the postnatal period for blood pressure control. The most commonly used antihypertenives were Labetalol, Nifedipine, Enalapril followed by Amlodipine, Hydralazine, Metoprolol and Prazosin.

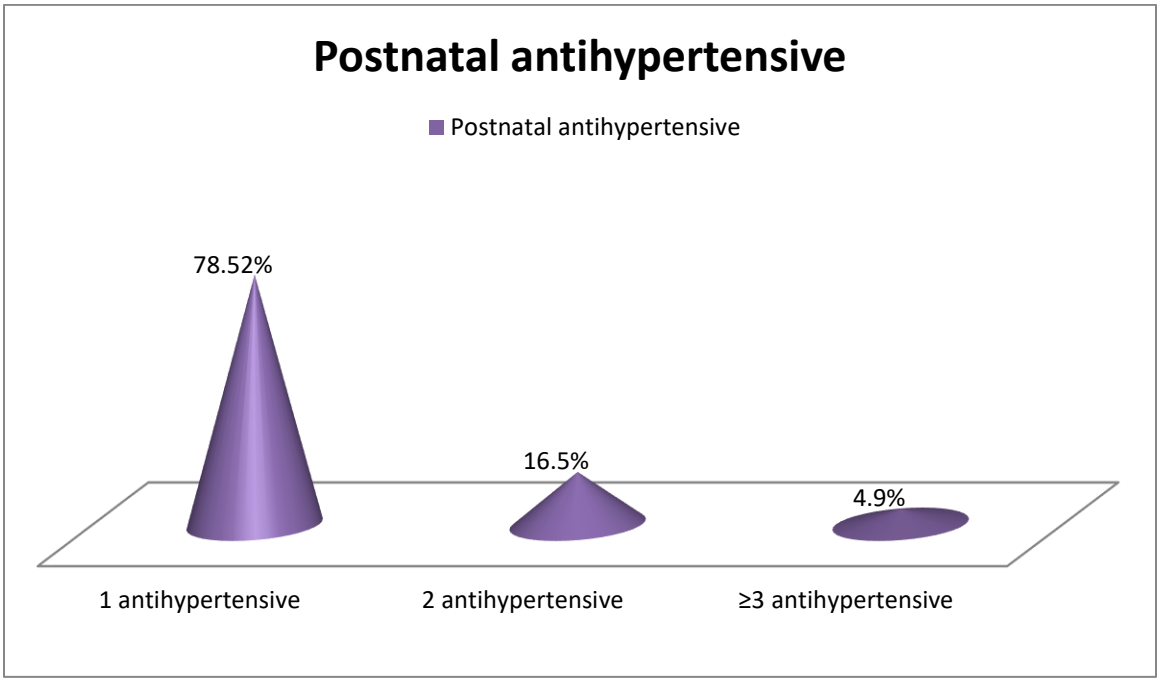


Fig.24 Postnatal antihypertensive

ICU admission:

Out of 400 women with hypertensive disorders of pregnancy, 8 women had ICU admission. Two women had ICU admission due to pulmonary edema and another two women had ICU admission due to difficulty in securing airway and difficult extubation following general anesthesia for cesarean section. Disseminated intravascular coagulation & massive blood loss was found in one woman who needed ICU care.

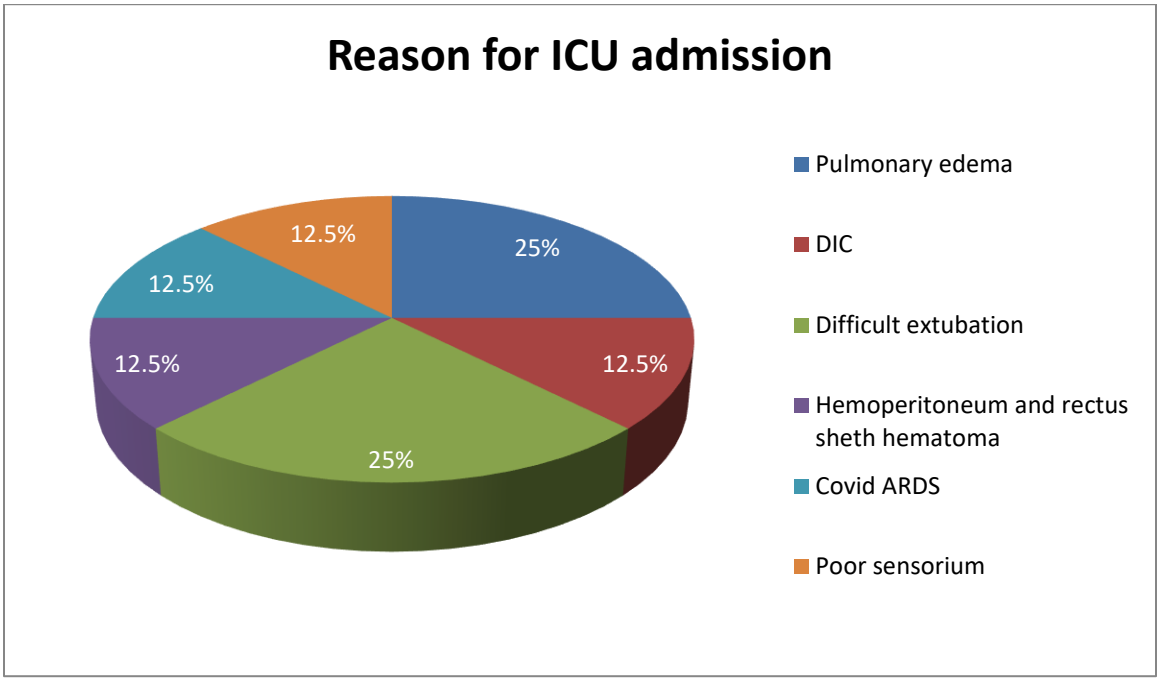


Fig.25 Reason for ICU admisison

Neonatal Outcome:

95%(n=380) were liveborn babies, 3%(n=12)were intrauterine fetal demise, 1.75% (n=7) were stillborn babies and 0.25% (n=1) was early neonatal death

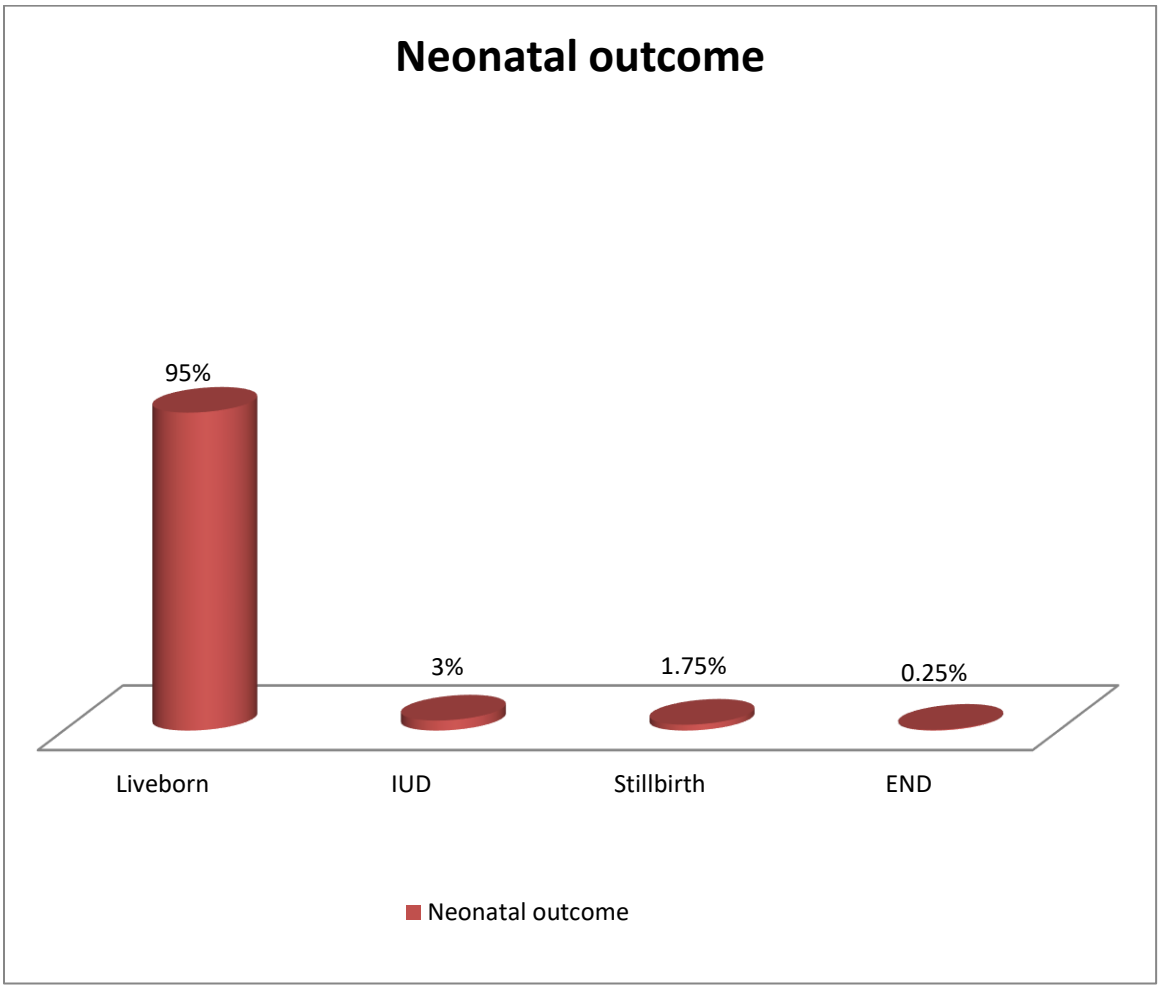


Fig.26 Neonatal outcome

APGAR Score:

Among the 381 babies which were born alive, including one baby which had early neonatal death, 90.28%(n=344) babies had APGAR score ≥7 at 1 minute and 9.71%(n=37) babies had APGAR score less than 7 at 1 minute.

At 5 minute, 98.95%(n=377) babies had APGAR score ≥ 7 and 1.04 %(n=4) had APGAR score less than 7.

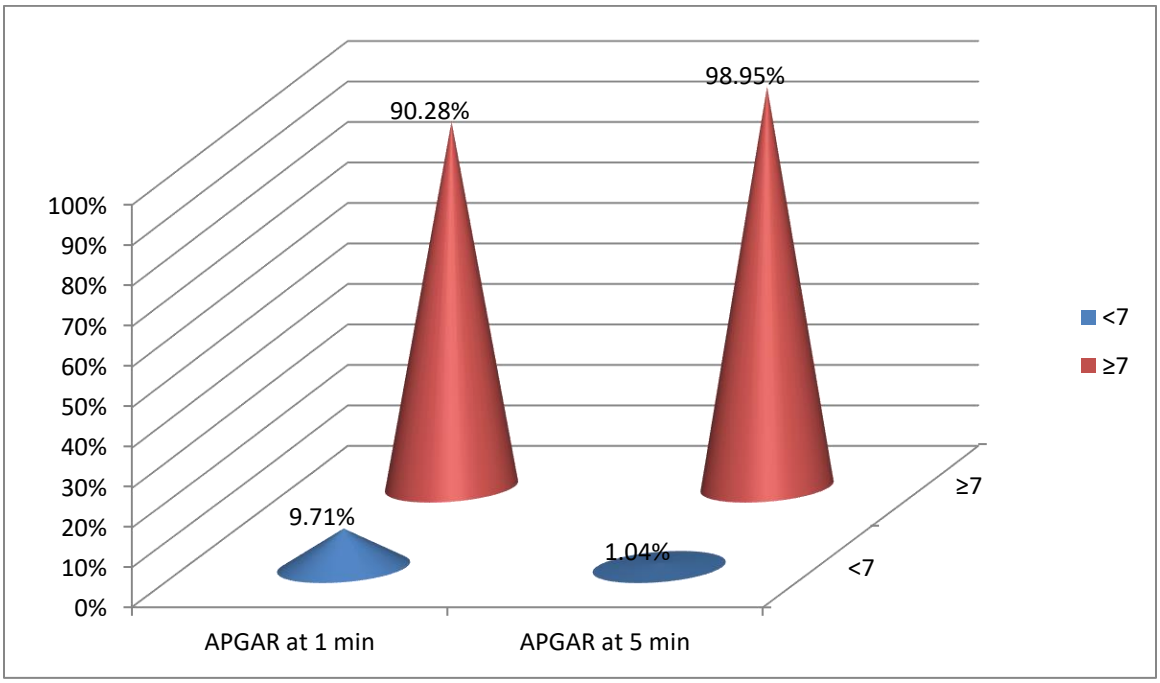


Fig.27 APGAR Score

Weight of the baby:

29%(n=116) of the babies born to the mothers with hypertensive disorders of pregnancy were between 2501 grams and 3000 grams followed by 23.3% (n=93) babies with birth weight more than 3000 grams.

22%(n=88) had birth weight between 2001 grams and 2500 grams and 11.5%(n=46) had birth weight between 1501 grams and 2000 grams.

9.5%(n=38) had very low birth weight that is between 1001 grams and 1500grams followed by 4.7 %(n=19) babies with extremely low birth weights that is less than 1000 grams.

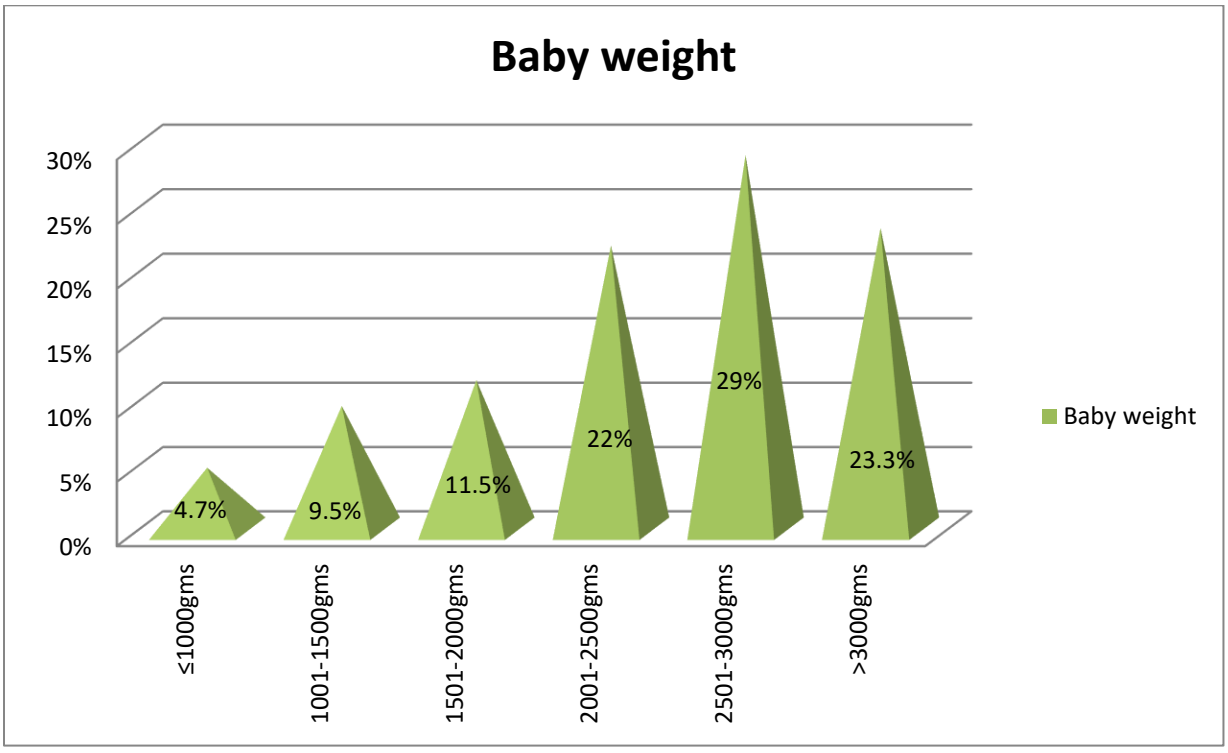


Fig.28 Weight of the baby

Neonatal complications:

Out of 381 babies which were born alive, including one baby who had early neonatal death, 41.99%(n=160) had low birth weight and 30.70%(n= 117) were preterm.14.69% (n=56) of babies had fetal growth restriction followed by 11.02%(n=42) of respiratory distress syndrome and 0.26% (n=1)had meconium aspiration syndrome.

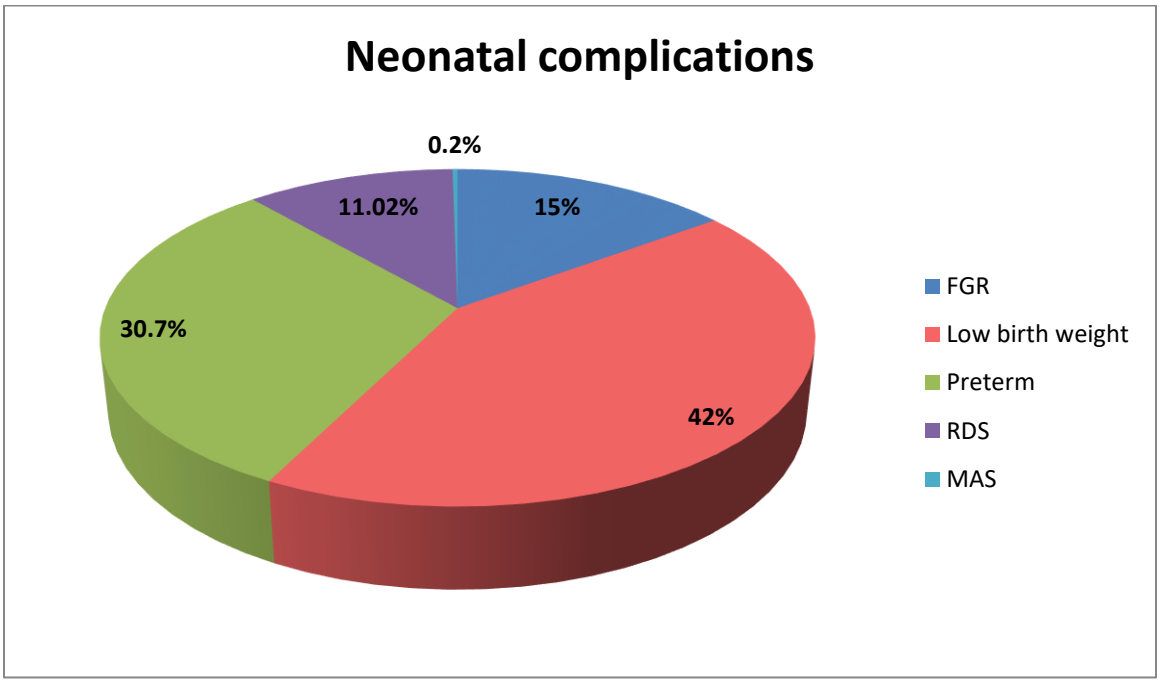


Fig.29 Neonatal complications

NICU admission:

Among the 381 babies who were born alive, 167 babies (43.83%) required NICU admission.

Prematurity was the commonest indication for NICU admission accounting to 58.6% (n=98).Respiratory distress was the second most common indication amounting to 14.3 %(n=24). 3.6%(n=6) babies born to the mothers with hypertensive disorder required NICU admission as they were depressed at birth. Various other causes for NICU admission were low birth weight (4.1%), hypoglycemia (5.3%), neonatal hyperbilirubinemia(6.5%), risk of sepsis(2.9%), neonatal seizure(0.5%). Few other indications were also found like suspected cardiac disease, Down's phenotype, Hirschprung's disease, neonatal thrombocytopenia and pneumonia.

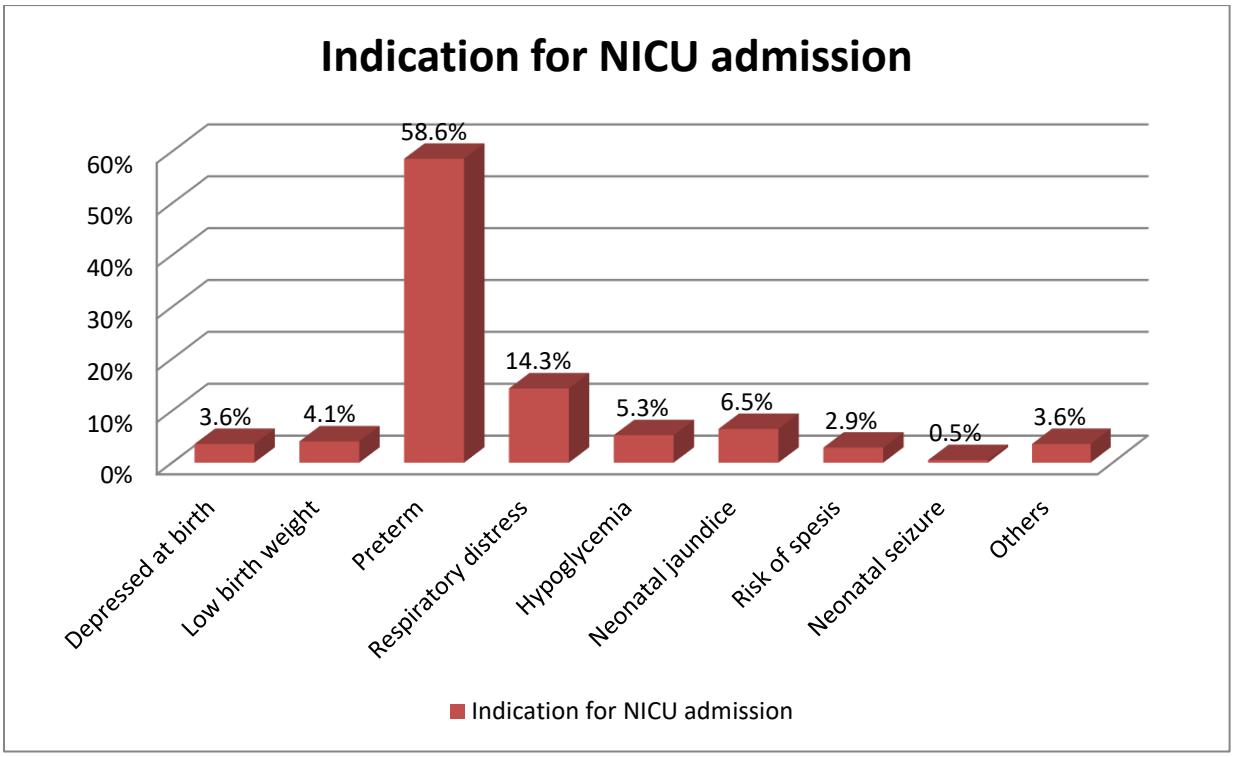


Fig .30 Indication for NICU admission

Demographic characteristics and risk factors for hypertensive disorder of pregnancy compared between 3 groups: 1.Gestational hypertension, non severe preeclampsia, 2.Severe preeclampsia, eclampsia and chronic hypertension with superimposed preeclampsia and 3. Chronic hypertension:

In all three groups, the majority of women were between 19 to 35 years of age. Primigravidas were more affected in those with gestational hypertension and preeclampsia but in those with chronic hypertension, there was no association with parity. Obesity was found to be high in chronic hypertension group compared to other two groups (p value = 0.001).

	Gestational HTN and non severe preeclamspsia N=157,N(%)	Severe preeclamspsia, eclampsia and chronic HTN with superimposed preeclamspsia N=203,N(%)	Chronic HTN N=40,N(%)	P-Value
Age ≤18 years 19-35 years >35 years	 3(1.9) 147(93.6) 7(4.4)	 5(2.4) 189(93.1) 9(4.4)	 0(0) 36(90) 4(10)	0.510
Parity Primigravida Multigravida	 99(63) 58(36.9)	 138(67.9) 65(32)	 20(50) 20(50)	0.088
Family history of HTN	57(36.3)	56(27.5)	16(40)	0.116

Obesity	28(17.8)	26(12.8)	15(37.5)	0.001

Tab.3 Demographic characteristics and risk factors

Comparison of the need for antihypertensives between 3 groups:

The need for antihypertensive was found be high in severe preeclampsia and chronic hypertension groups compared to non-severe group (p value < 0.001). This trend continued in the postnatal period where the requirement was less in gestational hypertension and non-severe preeclampsia group but remained high in other two groups (p value < 0.001)

Antihypertensives	Gestational HTN and non severe preeclamspsia N=157,N(%)	Severe preeclamspsia, eclampsia and chronic HTN with superimposed preeclampsia N=203,N(%)	Chronic HTN N=40,N(%)	P-Value
Antenatal Yes	98(62.4)	186(91.6)	31(77.5)	< 0.001
Postnatal Yes	76(48.4)	181(89.1)	26(65)	< 0.001

Tab .4 Need for Antihypertensives in the antenatal and postnatal period among the three groups

Comparison of the onset of labour and mode of delivery:

The rate of induction was found to significantly high in all three groups. The rate of LSCS was high in severe preeclampsia, eclampsia and chronic hypertension with superimposed preeclampsia.

	Gestational HTN and non severe preeclamspsia N=157,N(%)	Severe preeclamspsia, eclampsia and chronic HTN with superimposed preeclampsia N=203,N(%)	Chronic HTN N=40,N(%)	P-Value
Onset of labor Spontaneous Induction Not in labour	 17(10.8) 122(77.7) 18(11.4)	 12(5.9) 131(64.5) 60(29.5)	 3(7.5) 32(80.0) 5(12.5)	< 0.001
Mode of delivery Normal Vacuum Forceps LSCS	 70(44.8) 5(3.2) 27(17.3) 54(34.6)	 48(23.6) 2(0.9) 21(10.3) 132(65)	 9(23) 2(5.1) 7(17.9) 21(53.8)	< 0.001

Tab.5 Onset of labour and mode of delivery

Comparison of maternal complications between the groups:

Most of the complications were found to be more in severe preeclampsia, eclampsia and chronic hypertension with superimposed preeclampsia but was not statistically significant except for Partial HELLP which was found to be statistically significant (P value = 0.009). Also the 8 women who had ICU admission, belonged to the same group (P value=0.019).

Maternal complications	Gestational HTN and non severe preeclamspsia N=157,N(%)	Severe preeclamspsia, eclampsia and chronic HTN with superimposed preeclampsia N=203,N(%)	Chronic HTN N=40,N(%)	P-Value
HELLP syndrome	0(0)	5(2.4)	1(2.5)	0.14
Partial HELLP	1(0.6)	12(5.9)	0(0)	0.009
Placental abruption	7(4.4)	8(3.9)	0(0)	0.407
DIC	(0)	1(0.4)	0(0)	0.615
PPH	21(13.3)	19(9.3)	3(7.5)	0.372
Pulmonary edema	0(0)	4(1.9)	0(0)	0.141

Acute renal failure	0(0)	3(1.4)	1(2.5)	0.227
PRES	0(0)	3(1.4)	0(0)	0.231
ICU admission	0(0)	8(3.9)	0(0)	0.019

Tab .6 Maternal complications

Comparison of the neonatal outcomes between the groups:

Most of the women with hypertension complicating pregnancy had a livebirth. Stillbirth and early neonatal death was noted in severe preeclampsia, eclampsia and chronic hypertension with superimposed preeclampsia group but the difference was not statistically significant.

Neonatal outcome	Gestational HTN and non severe preeclamspsia N=157,N(%)	Severe preeclamspsia, eclampsia and chronic HTN with superimposed preeclampsia N=203,N(%)	Chronic HTN N=40,N(%)	P-Value
Liveborn IUD Still birth END	152(96.8) 5(3.1) 0(0) 0(0)	190(93.6) 5(2.4) 7(3.4) 1(0.4)	38(95.0) 2(5.0) 0(0) 0(0)	0.190

Tab .7 Neonatal outcome

Comparison of neonatal complications between the 3 groups:

The incidence of fetal growth restriction (p =0.012), low birth weight (p<0.001) and prematurity (p<0.001) was significantly high in severe preeclampsia, eclampsia and chronic hypertension with superimposed preeclampsia. Respiratory distress syndrome was also high in the same group but was not found to be statistically significant.

Neonatal complications	Gestational HTN and non severe preeclamspsia N=152,N(%)	Severe preeclamspsia, eclampsia and chronic HTN with superimposed preeclampsia N=191,N(%)	Chronic HTN N=38,N(%)	P-Value
FGR	13(8.5)	38(19.9)	5(13.1)	0.012
LBW	35(23)	117(61.2)	8(21)	< 0.001
Preterm	16(10.5)	97(50.7)	4(10.5)	< 0.001
RDS	13(8.5)	26(13.6)	3(7.8)	0.268
MAS	1(0.6)	0(0)	0(0)	0.470

Tab 8.Neonatal complications

DISCUSSION

We recruited 400 women with hypertensive disorders of pregnancy admitted in Labour Room and Obstetric Ward after informed written consent. Those included in the study were observed for mode of delivery, maternal complications and outcome, perinatal complications and outcome.

Though the risk of hypertensive disorders in pregnancy increases with age over 35 years according to Liu et al (147) , in our study we found that women belonging to age group between 19 and 35 years have maximum incidence of hypertensive disorder of pregnancy. The same was reported by Singh Poojah et al with highest incidence among 21-30 years of age (69.4%).(148)

Concerning parity, the incidence was more in primigravidas. This was in accordance to the study by Meazaw et al in which they found that primiparous women had twofold increased odds of developing hypertensive disorder of pregnancy compared to multiparous women.(149)The same association was found by Hinkosa et al as well.(150)

Diabetes mellitus was the most common medical co-morbidity found in our study. A study conducted by Singh et al found that pregnant women with diabetes were five times more likely to develop hypertensive disorder of pregnancy in comparison to women without diabetes mellitus.(151) Similarly, another two studies from Ethiopia by Kahsay et al and Hinkosa et al also reported that the odds of developing hypertensive disorder of

pregnancy was 5.4 and 5.03 times higher among diabetic mothers when compared to non-diabetic mothers respectively.(150,152)

Anemia in pregnancy was associated with higher risk of hypertensive disorder .16.25% of women with hypertensive disorder of pregnancy had anemia in our study. This was in accordance with a study by Rohilla et al where 17.7% of women with severe anemia had gestational hypertension or preeclampsia and 2.1% had eclampsia.(153) A study by Ali et al showed women with severe anemia had a 3.6 times higher risk of preeclampsia. (154)

Other medical comorbidities found in our study were bronchial asthma, hypothyroidism, seizure disorder, renal disorders like nephrotic syndrome and chronic kidney disease, autoimmune diseases like APLA, SLE, autoimmune hemolytic anemia, Takayasu arteritis and thrombotic thrombocytopenic purpura.

We noted in our study that 32.5% of the women with hypertensive disorder of pregnancy had a family history of hypertension. A study conducted by Mekonen et al reported that the women with a family history of preeclampsia were six times more likely to develop hypertensive disorder of pregnancy.(155) Another study by Owiredu et al also reported women with family history of hypertension had seven times higher odds of developing hypertensive disorder of pregnancy. (156)

Obesity is another risk factor for hypertensive disorder of pregnancy.17.25% of women with hypertensive disorder of pregnancy in our study were obese and it was a statistically significant risk factor for all types of hypertensive disorder of pregnancy. Singh et al also

found that obese women were nearly three times more likely to develop hypertensive disorder of pregnancy compared to women with a normal BMI.(151)

31% of women in our study had history of hypertension in their previous pregnancy. The same was reported by Tebeu et al's study where 31% mothers had a history of hypertension during a previous pregnancy, that is equal to sevenfold increased risk of developing hypertensive disorder of pregnancy.(157)

In our study, 78.75% and 71% of women required antihypertensive agents for blood pressure control during the antenatal period and the postnatal period, respectively. The predominant antihypertensive agents used were labetalol and nifedipine. Panda et al in their study reported the use of antihypertensives in all the 402 women with hypertensive disorder of pregnancy included in the study.(99) In a study by Easterling which was aimed to compare the efficacy and safety of three oral drugs, labetalol, nifedipine retard and methyldopa for the management of severe hypertension in pregnancy, it was found that all the three oral antihypertensives reduced blood pressure to the reference range in most women and nifedipine retard resulted in a greater frequency of lowering blood pressure within 6 hours of administration than labetalol or methyldopa use. (158)

About 60 % of the women in our study had delivery at term and postdates. The onset of labour was by induction for 71.7% with majority of induction being related to hypertension. Prostagladin (PGE 1) and Foley's were the common modes of induction used. According to Sonnaville et al, as HYPITAT-I trial showed that induction of labor was associated with improved maternal outcome without compromising neonatal

outcome in women with gestational hypertension or mild preeclampsia at term, the rate of induction of labor increased from 51.1% before the HYPITAT-I trial to 64.2% after it.(159)

The mode of delivery was through cesarean section for majority of women in our study accounting to 51.7% followed by normal vaginal delivery in 32.25% and instrumental delivery in 16%. IS Sapna et al also found that common mode of delivery was caesarean section accounting to 72.6%.(160) In contrast, 67.5% patients delivered by vaginal route followed 32.5% by LSCS in a study by Joshi et al. (40) The commonest indication for LSCS in our study were non reassuring fetal status, deteriorating maternal condition and failed induction.

The most common maternal complication seen in our study was postpartum hemorrhage followed by eclampsia. Placental abruption was seen in 3.7% of women and partial HELLP syndrome in 3.25% followed by HELLP syndrome in 1.5%.Other complications seen were pulmonary edema, acute renal failure, PRES and DIC. Most of the complications were majorly seen in women with severe preeclampsia, eclampsia and preeclampsia superimposed on chronic hypertension. Similarly in a study by IS Sapna et al ,maternal complications were noted in 29.5% of women which was attributed to renal dysfunction, postpartum haemorrhage, DIC, placental abruption, HELLP, pulmonary oedema.(160)

In our study, 3% had intrauterine death, 1.7% were stillborn babies and one baby had early neonatal death. Also 1% of babies had APGAR score less than 7 at 5min and 43.8%

needed NICU care. According to Singh et al, intrauterine deaths were recorded among 12.2% and a majority of fetuses (41.2%) were diagnosed to have intrauterine growth restriction.(148) Low birth weight was the most common neonatal complication seen accounting to seen in 41.9% followed by preterm, fetal growth restriction and respiratory distress syndrome in our study. This was in accordance to a study by Uwizeyimana et al in which low birth weight was the most common neonatal complication accounting to 75.4% followed by prematurity and fetal growth restriction. Also 59.6% required admission to neonatal intensive care unit in that study.(108)

CONCLUSION

Hypertensive disorders of pregnancy are a major cause for maternal and perinatal morbidity and mortality which was more common in women with severe preeclampsia, eclampsia and preeclampsia superimposed on chronic hypertension.

The induction rate was high in women with hypertensive disorder of pregnancy, with the majority of the induction being related to hypertension. Although the presence of a hypertensive disorder of pregnancy by itself is not an indication for cesarean delivery, majority of women had delivery through cesarean section with commonest indications being non reassuring fetal status, deteriorating maternal condition and failed induction.

Adequate awareness and education among the high risk women concerning potential associated risk factors like obesity, family history of hypertension, previous pregnancy with hypertension, comorbidities like diabetes, renal disease, autoimmune diseases and management is essential. Also timely intervention and early referral to tertiary care centers is necessary to improve outcome.

The decision concerning the timing of delivery by weighing the maternal and fetal risks of prolonging the pregnancy versus the potential benefits of further fetal maturation might be crucial to reduce complications. Early diagnosis, regular antenatal checkup, close monitoring of both the baby and the mother, early initiation of antihypertensive agent and timely delivery may significantly improve the maternal and perinatal outcome.

LIMITATIONS

The main limitation of the study was that the study subjects and the neonates were followed up only for immediate complications and not for long term complications. Secondly, this study is done in a tertiary care center. So it does not show the outcomes in low resource setting. The women were recruited when they were admitted for delivery. Hence awareness and education concerning the complications and management of hypertensive disorders of pregnancy was not done.

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ANNEXURES

ANNEXURE I - INSTITUTIONAL REVIEW BOARD APPROVAL

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, MD., Ph.D.,
Chairperson,
Research Committee & Principal

Dr. Suceena Alexander, MD., DM., FASN.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

May 30, 2020

Dr. Monitta M,
PG Registrar,
Department of OG-3,
Christian Medical College,
Vellore – 632 002.

Sub: Fluid Research Grant: New Proposal:
Maternal and perinatal outcomes in hypertensive disorders of pregnancy
Dr. Monitta M, Post Graduate Registrar, Obstetrics and Gynecology, Dr. Preethi.R.N, Dr.Annie Regi, Dr.Anuja Abraham, Dr. Kavitha Abraham, OG, Dr.B. Antonisamy, Biostatistics.

Ref: IRB Min. No. 12609 [OBSERVE] dated 05.02.2020.

Dear Dr. Monitta M,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Suceena Alexander, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Suceena Alexander
Secretary (Ethics Committee)
Institutional Review Board

Dr. Suceena Alexander, MD.,DM.,FASN.
Secretary - (Ethics Committee)
Institutional Review Board
Christian Medical College,
Vellore - 632 002, Tamil Nadu, India.

Cc: Dr. Preethi.R.N, OG - 3, CMC, Vellore

1 of 5

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

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Ref: IRB Min. No. 12609 [OBSERVE] dated 05.02.2020.

Dear Dr. Monitta M,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Maternal and perinatal outcomes in hypertensive disorders of pregnancy" on February 05, 2020.

The Committee reviewed the following documents:

1) IRB application format
2) Patient information sheet and Consent Form (English, Tamil, Telugu)
3) Proforma
4) Permission Letters
5) Cvs. Of Drs. Antonisamy, Kavitha Abraham, Annie Regi, Anuja, Monitta, Preethi.
6) No. of documents 1- 4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on February 05, 2020 in the New IRB Room, Christian Medical College, Vellore 632 004.

2 of 5

Dr. B.J. Prashantham, M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, MD., Ph.D.,
Chairperson,
Research Committee & Principal

Dr. Suceena Alexander, MD., DM., FASN.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. B. J. Prashantham	MA (Counseling Psychology), MA(Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Suceena Alexander	MD, DM., FASN	Professor, Nephrology, Additional Vice Principal, Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. John Jude Prakash	MBBS, MD,	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Dr. Rekha Pai	MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal, Basic Medical Scientist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, Vellore	External Legal Expert
Dr. Barney Isaac	DNB (Respiratory Diseases)	Associate Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Joe Varghese	MBBS, MD Biochemistry	Professor, Department of Biochemistry	Internal Clinician
Dr. Santosh Varughese	MBBS, MD, DM, FRCP.	Professor, Head of the Department of Nephrology.	Internal Clinician

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Dr. Suceena Alexander, MD., DM., FASN.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Mrs. Nirmala Margaret	MSc Nursing	Addl. Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Balu Krishna	MBBS MD DNB DMRT	Professor, Department of Radiotherapy, CMC Vellore	Internal Clinician
Dr. HS. Asha	MBBS, DNB	Professor, Department of Endocrinology, CMC Vellore	Internal Clinician
Dr. Rohin Mittal	MS , DNB	Professor, Department of General Surgery, CMC Vellore	Internal Clinician
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Shyam Kumar NK	DMRD, DNB, FRCR, FRANZCR	Professor, Radiology, CMC, Vellore	Internal, Clinician
Dr. Winsely Rose	MD (Paed)	Professor, Paediatrics, CMC Vellore	Internal, Clinician
Mrs. Sophia V	M.Sc Nursing	Addl. Deputy Dean CMC, Vellore	Internal, Nurse
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "Maternal and perinatal outcomes in hypertensive disorders of pregnancy" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

The Institutional Ethics Committee expects to be informed about the progress of the project, Any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Chairperson,
Research Committee & Principal

Dr. Suceena Alexander, MD., DM., FASN.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Fluid Grant Allocation:

A sum of 30,000/- INR (Rupees Thirty Thousand Only) will be granted for 12 Months.

Yours sincerely,

Dr. Suceena Alexander
Secretary (Ethics Committee)
Institutional Review Board

Dr. Suceena Alexander, MD.,DM.,FASN.
Secretary - (Ethics Committee)
Institutional Review Board
Christian Medical College,
Vellore - 632 002, Tamil Nadu, India.

IRB Min. No. 12612 [OBSERVE] dated 05.02.2020

ANNEXURE-II

INFORMATION SHEET

CHRISTIAN MEDICAL COLLEGE, VELLORE
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

INFORMATION SHEET
STUDY TITLE : STUDY ON HYPERTENSIVE DISORDERS OF PREGNANCY

Dear_____
Greetings from Obstetrics department, CMC Vellore.
This is an observational study on hypertensive disorders of pregnancy. As you are diagnosed to have hypertension in pregnancy, you are requested to participate in the study. The study is only to observe you in the obstetric ward and labour room and follow up till delivery. No extra test or cost or any harm is rendered during this study as it is only observational. Indeed extra care is offered as you will be observed and monitored closely. Any complications to arise in meanwhile will be discussed with you in detail and treatment options will be discussed.
Being a part of the study, doesn't harm you or the baby in any way. However for some reason if you choose not to participate in the study or to withdraw from the study, you can choose that without your medical care being affected.

Address: Dr.Monitta,
Department of Obstetrics and Gynecology,
CMC Vellore.
Phone no.: 7598454485

ANNEXURE-III

CONSENT FORM

Informed Consent form to participate in a research study
Study Title*: OBSERVATIONAL STUDY ON OUTCOMES IN HYPERTENSIVE DISORDERS OF PREGNANCY*

Study Number:
Subject's Initials: _____ Subject's Name: _____
Date of Birth / Age:_____
(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]
(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]
(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]
(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]
(v) I agree to take part in the above study. [ ]
Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____
Date: _____/_____/_____
Signatory's Name: _____
Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____
Signature of the Witness: _____
Date:_____/_____/_____
Name of the Witness: _____

ANNEXURE IV

PROFORMA

PROFORMA: Maternal and perinatal outcomes in hypertensive disorders of pregnancy

Serial number:

Name: Age: Hospital number:

GA: Obstetric score:

Booked In/Out: ☐ 1 ☐ 2 Singleton or twins: ☐ 1 ☐ 2

LMP: EDD:

Other medical complication:

1. Heart disease 2.Diabetes 3.HIV 4.HbSAg 5. Anemia

6. Seizure disorder 7.Bronchial asthma 8. Hypothyroidism 9. Cholestasis of pregnancy

11. APLA 12. SLE 13. Others - Specify

Other Risk Factors :

1. Previous pregnancy with hypertensive disorders 2.Family history of HTN 3.Obesity

GA at diagnosis of hypertension:

Anti hypertensives: 1. Yes 2. No

Medications: 1. Labetalol 2. Nifedipine 3. Others - Specify

GA when antihypertensive was started:

1. ≤28 weeks 2. 28+1 to 30 weeks 3. 30+1 to 32 weeks 4. 32+1 to 34 weeks

5. 34+1 to 36 weeks 6. 36+1 to 37 weeks 7. 37+1 to 38 weeks 8. 38+1 to 39 weeks

9. 39+1 to 40 weeks 10. >40 weeks

Type of hypertensive disorder:

1. Gestational hypertension 2.Preeclampsia : a. Non severe b.Severe

3. Chronic hypertension 4.Preeclampsia superimposed on chronic HTN 5.Eclampsia

GA at delivery:

1. ≤28 weeks 2. 28+1 to 30 weeks 3. 30+1 to 32 weeks 4. 32+1 to 34 weeks

5. 34+1 to 36 weeks 6. 36+1 to 37 weeks 7. 37+1 to 38 weeks 8. 38+1 to 39 weeks

9. 39+1 to 40 weeks 10. >40 weeks

Onset of labour: 1.Spontaneous 2. Induction

Indication for induction: 1. HTN related 2.Non related Specify

Mode of induction: 1. PGE1 2.Foley's 3. Foley's and PGE1 4. Oxytocin

Mode of delivery:

1. Normal 2.Vacuum Indication:

3.Forceps Indication: 4. LSCS a. Elective b. Emergency

Indication for caesarean section:

1. Failed induction 2. NRFS 3. Deteriorating maternal condition

4. Arrest of dilatation 5. Malpresentation 6. Protracted dilatation

7. Arrest of descent 8. Cord prolapse 9. Previous LSCS

10. Others Specify

Maternal complications:

1.HELLP Syndrome 2.Partial HELLP 3. Acute Respiratory Distress Syndrome

4. Placental abruption 5.DIC 6. Post parum hemorrhage

7. Pulmonary edema 8.Acute Renal Failure 9.PRES

10. Cerebrovascular Accident 11.Eclampsia a.Antepartum b.Peripartum c.Postpartum

12.Peripartum cardiomyopathy 13. Maternal death

Total blood loss: 1. <500ml 2. 500-1000ml 3. >1000ml

Postnatal anti hypertensives: Yes 1 No 2 If yes,drugs:

No. of days of hospital stay:

ICU admission: 1. Yes 2. No If yes,reason:

Neonatal outcome:

1. Liveborn 2. IUD 3. Still birth 4. Early Neonatal death

Baby's hospital number:

APGAR at 1 min 5 minute

Weight in grams: Sex: Male 1 Female 2

Neonatal complications:

1. Fetal growth restriction 2. Low birth weight 3. Preterm 4. Respiratory distress syndrome

5. Meconium aspiration

NICU admission: Yes 1 No 2 If yes,indication:

ANNEXURE V -MASTER SHEET