



## Treatment of Hypertension during Pregnancy and Lactation

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### ABSTRACT

We all know due to the sedentary Lifestyle that all are sustaining, get exposed to many diseases and one of the serious diseases is hypertension. But this hypertension gets heavy-handed when it happens to a pregnant lady because it's not only risking the life of the mother but also risks the life of the infant. Then the infant can get affected due to many reasons like the medications, high blood pressures, teratogenicity, etc. Around 6-8% of the pregnant population gets affected due to hypertension. The normal blood pressure in pregnant women should be 140 mm HG for systolic and 90 mm HG for diastolic. If the blood pressure exceeds from this like for example it reaches till 160 mm HG for systolic and 110 mm HG for diastolic then it's a lot alarming for the patient. For the treatment of hypertension in pregnancy the most commonly used antihypertensive drugs are beta blockers, calcium blockers, vasodilators. From beta-blockers labetalol and propranolol which are widely used, from vasodilators hydralazine and from calcium blockers nifedipine frequently prescribed medicine. Above all the medications the first line of treatment is by the methyldopa medications. Extreme care needs to be taken in the period of Postpartum and breastfeeding. To make the judgement of drug concentration more accurately for the well-being of the Infant scientists use the term M/P ratio. The most widely used or the first-line treatment is given through the ACE inhibitors like Enalapril and Captopril.

**Keywords:** Gestational Hypertension, Pre-eclampsia, Postpartum, Lactation, M/P ratio.

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- White-coat hypertension
- Preeclampsia superimposed on chronic hypertension
- Gestational hypertension

Chronic hypertension is usually before pregnancy or before 20 weeks of gestation. It can be diagnosed before during or after the pregnancy. This type of hypertension can be with or without proteinuria. The systolic blood pressure is more than 140 mm HG and the diastolic is more than 90 mm HG, almost 3 to 8% of the maternal population get affected due to chronic hypertension. Chronic hypertension can also persist after postpartum.<sup>[4]</sup>

Preeclampsia is the hypertension which is accompanied with endothelial disorders, proteinuria (0.3 grams or more of protein in a 24 hour urine collection), acute kidney injury (creatinine  $\geq 90 \mu\text{mol/L}$ ; 1 mg/dL), elevated transaminases (aspartate aminotransferase  $>40 \text{ IU/L}$ ), neurological complications, haematological complications like thrombopenia (platelet count  $<1,50,000/\mu\text{L}$ ) and placenta dysfunction (such as fetal growth restriction, abnormal umbilical artery [UA] Doppler wave form analysis, or stillbirth).<sup>5,6</sup> This condition has the risk of almost 2 to 5% of the maternal population.<sup>7</sup>

White coat hypertension is a type of hypertension condition where there is elevation in the clinical BP ( $\geq 140/90 \text{ mm Hg}$ ) and a regular blood pressure during self-monitoring ( $<135/85 \text{ mm Hg}$ ). This condition is usually diagnosed before or after the 20th week of gestation. A

### INTRODUCTION

All over the globe there has been a great argument regarding the classification, diagnosis, treatment, and management of hypertension during pregnancy. This results in lack of awareness and treatment for the needy. After a lot of researches, the scientist has tried to define these disorders, suggest prevention towards it and treatment too.

There are enormous hemodynamic changes during pregnancy. The Mother's blood volume starts to rise by the fifth week of gestation and by the end of pregnancy the blood volume increases upto 50%. Around 6 to 8% of pregnant women population is estimated to get diagnosed with hypertension during their pregnancy.<sup>1-3</sup>

Hypertension in pregnancy includes a broad class of conditions as following:

- Chronic hypertension
- Pre-eclampsia



persistent in white coat hypertension can result in preeclampsia.<sup>8,9</sup>

Gestational hypertension is also known as pregnancy-induced hypertension which usually occurs after 20<sup>th</sup> week of gestation. This hypertension is different from chronic hypertension and preeclampsia as in this condition there is no symptoms of proteinuria. But this condition may also lead to preeclampsia.<sup>10,11</sup> The blood pressure readings are used to higher than 140/90 mmHG. After the pregnancy does hypertension usually terminates.<sup>12</sup>

Preeclampsia superimposed on chronic hypertension is a case when a pregnant woman who is already suffering from chronic hypertension get superimposed preeclampsia. This condition is usually higher among the women who are already suffering from renal disease. The reading of proteinuria in such patients are usually higher than the usual readings before pregnancy. This condition again occurs after 20<sup>th</sup> week of gestation.<sup>13</sup> There might be fetal growth restriction. The only difficulty lies here is preeclampsia superimposed on chronic hypertension is difficult to distinguish when diagnosed.<sup>14</sup>

### Etiology

Almost 10% of the pregnant women population is affected by hypertension during the pregnancy. There are several reasons for, out of chronic hypertension is one of the most prominent reasons. Development of hypertension during pregnancy can be less harmful but at times can leave to persistent hypertension after the pregnancy also. Following are few of the aetiology for hypertension during pregnancy:

- Proteinuria: the level of creatinine Rises over 30 mg/mmole
- Maternal organ dysfunction:
  - a. acute kidney disease where the creatinine level reaches more than 90 mg/mmol

- b. Liver dysfunction where there is elevated level of alanine aminotransferase.
- c. Neurological complications
- d. haematological complications for example intravascular coagulation, haemolysis decrease platelet count<sup>15,16</sup>

- Uteroplacental dysfunction
- Hyperaldosteronism
- Cushing's syndrome
- Hyperparathyroidism<sup>17</sup>

### Drugs Used for Its Treatment

#### Labetalol

Labetalol is a synthetic drug which is used to treat hypertension. This drug has gained a wide acceptance in pregnancy because it is non selective  $\beta$  blockers with vascular  $\alpha_1$  receptors blocking capabilities. It is an adrenergic receptor blocker specifically blocking  $\beta_1$ ,  $\beta_2$  and  $\alpha_1$  it is believed to have hundred percent oral bioavailability lies between 30 to 40%. It has a half-life of 5.528 hours and protein binding up to 50%. When it comes to excretion 55 to 60% is excreted in urine as conjugates or unchanged drugs. It is a combined alpha and beta receptor antagonist with vasodilatory effects that can decrease blood pressure in pregnancy without compromising utero placental blood flow. It is suggested as the first-line agent of treatment for non-severe hypertension in pregnancy.<sup>18, 19</sup>

Labetalol is considered to be given if Rapid BP control is desired. It is usually given in the form of parentals. It is considered to be safe for chronic hypertension and is effective as methyldopa. This drug can also be used on the direct vasodilator. The concentration of labetalol in the breast milk is way lower than the rest of the beta blockers.

**Table 1:** Clinical findings or symptoms of the most commonly seen hypertensions in pregnancies.

Sr. No	Clinical finding	Chronic Hypertension	Gestational Hypertension	Preeclampsia
1.	Onset of hypertension	<20 week of gestation	Usually in third trimester	>20 Weeks of gestation
2.	Range of hypertension	Mild or severe	Mild	Mild or severe
3.	Liver dysfunction	Absent	Absent	Present in severe disease
4.	Decrease of platelet count	Absent	Absent	Present in severe disease
5.	Proteinuria*	Absent	Absent	Usually, present
6.	Hemoconcentration	Absent	Absent	Present in severe disease
7.	Symptoms	Pre-existing hypertension	Blood pressure elevated > 140/90 mm Hg	Blood pressure elevated > 140/90 mm Hg and +1 or greater proteinuria on dipstick
Proteinuria- presence of excess protein in the urine				



**Table 2:** The most frequently used drugs for treatment according to their preference.

Sr. No	Indication	Drug Name	Dose	Contraindication	Time of onset	Use in breastfeeding
1.	First-line	Labetalol	100-800mg TDS	Asthma, decompensated heart failure	2-4 hours	Yes
2.	Second-line	Nifedipine MR tablets	10-40mg BD	Immediate release and sublingual preparations are not used in UK due to unpredictable hypotensive effect	1.5-4.2 hours	Yes
3.	Third-line	Methyldopa tablets	250mg- 1g TDS	Liver dysfunction mood disorder	6-9 hours	Yes
3.	Third-line	Methyldopa tablets	250mg- 1g TDS	Liver dysfunction mood disorder	6-9 hours	Yes
4.	Fourth-line	Doxazosin tablets	2-16mg total daily dose	Postural hypotension	2-3 hours	Probably compatible
		Labetalol infusion	20mg/hour titrated (double, maintain or halves) as required every 30 minutes to a maximum dose of 160 mg/hour	Asthma, decompensated heart failure	5-10 minutes	
		Hydralazine infusion	5mg/hour, titrated to blood pressure	Maternal tachycardia (heart rate > 120 bpm)	15-30 minutes	
5.	Postpartum only	Enalapril (preferred)	2.5-10 mg BD orally	Contraindicated in pregnancy, Hyperkalaemia, Acute kidney injury	4-6 hours	Yes

The concentration of drug in the human milk is considered to be below and is compatible with breastfeeding and the health of the infant. The mechanism of action for labetalol is like the drug moieties bind up to the adrenal nervous system which leads to expansion and increase in the diameter of arteries hence decreasing the blood pressure. Labetalol is considered to be more effective on  $\beta$  receptors than on  $\alpha_1$  blocking agent almost 6.9 times more than it.<sup>20</sup>

In maximum cases of labetalol, it is well tolerated by the patients. Its adverse effects are nausea, vomiting, bronchoconstriction, dizziness, heart block and static hypotension. It is believed to have negative inotropic effect and has the potential to cause acute left ventricular failure.<sup>21</sup>

#### Atenolol

Atenolol is the  $\beta$ -adrenergic receptor blocker having the full extent of adsorption up to 50 percent with 50 to 60% of absolute oral bioavailability and the half-life of 5 to 6 hours. The extent of protein binding is up to 16% and is believed to be 50% excreted unchanged in the feces.

Atenolol belongs to a class of drugs known as Beta blocker it works by blocking the action of certain chemicals like NE (Norepinephrine). It blocks the receptors by competitive inhibition and is considered to be more hydrophilic. It does not act via vasodilation. Due to more hydrophilicity the drug cannot cross the blood brain barrier and does not

show any dizziness. This affects lowers the heart rate blood pressure and strain on the heart.<sup>22, 23</sup>

Atenolol is highly recommended in the second trimester of pregnancy. It is also useful when patients with pre-existing hypertension. This drug appears to be safe for use in hypertension pregnancy. This drug is not recommended for breastfeeding mothers.<sup>24</sup>

The amount of Atenolol found in the human milk is high enough to cause harm to the infant. The drawbacks of Atenolol are decrease in the fetal growth, decrease in the uteroplacental blood flow main cause for short to medium term paediatric complications. If this drug is administered during the first trimester, then the baby is born with low birth weight.<sup>25,26</sup>

#### Metoprolol

Metoprolol is a cardio selective  $\beta$ -adrenergic receptor antagonist which is used to treat hypertension in pregnant women with cardiovascular diseases including cardiomyopathy, ischemic heart and arrhythmia.

Metoprolol is  $\beta_1$  selective adrenergic receptor blocker. It can be observed up to 95% of oral absorption with absolute bioavailability of 77%. It has got the half-life of 3-7 hours with protein binding up to 12%. It is excreted via hepatic and renal excretion in less than 5% and change form.<sup>27,28</sup>



Metoprolol is highly recommended in the first trimester and is usually given as the first line of treatment. Metoprolol decreases the blood pressure by negative inotropic and chronotropic effect. It reduces the heart rate and cardiac output. Since metoprolol is highly lipophilic in nature, it has got the tendency to pass via plasma into the human milk due to this reason metoprolol is not suggested to patients undergoing breastfeeding. This drug has got accumulation in the human milk and can cause adverse effect to the infant.<sup>29, 30</sup>

Metoprolol has got an advantage over rest of the beta blockers as it does not bring any previous mortality and has a decrease in the fetal growth retardation.

#### **Timolol**

Timolol is  $\beta_1$  and  $\beta_2$  selective adrenergic blocker. They get absorbed up to 90% and have absolute oral bioavailability of about 75%. It has got the half-life of four hours and protein binding up to 10%. For excretion it acquires hepatic and urinary excretion mostly in the form of its metabolites or unchanged drug. They work by increasing the level of cyclic amp. This drug is also used to treat diseases like glaucoma and can be suggested with patients undergoing breast feeding.<sup>31</sup>

#### **Methyldopa**

Methyldopa is a crude drug which acts on  $\alpha_2$  as an agonist via its active metabolite Alpha methyl norepinephrine. The active metabolite of methyldopa is hydrophilic in nature and hence both are unable to pass the blood brain barrier layers whereas the methyldopa is able to pass the BBB as it is more lipophilic in nature. It is centrally acting sympatholytic agents. This drug is too much available in the L-isomer. This drug is well absorbed orally and has got a half-life of 2 hours. This drug usually doesn't alter the cardiac function to a great extent for this reason this needs to be taken regularly at a long-term use.<sup>32</sup>

Methyldopa can be given intravenous or oral routes. This drug can start its action within 1 to 2 hours and is effective up to two to six hours. The active metabolite of methyldopa has the tendency to cross placental barrier causing fetal serum concentration similar to those in the mother.<sup>33</sup>

Methyldopa is frequently used as the first line and third line of treatment for Hypertension in pregnancy. This drug is prescribed during the early and later stages of gestation and most probably in the third trimester.

Methyldopa is considered to be safe in pregnancy as well as for breastfeeding as very low traces of this drug has been found in the human milk. It also remains the first drug of choice in the chronic hypertension taking place in the pregnant patients.<sup>34</sup> In maximum of the cases this drug is been tolerated well but still there are few adverse effects like elevated liver enzymes by 5%, hepatitis and hepatic necrosis.

#### **Nifedipine**

Nifedipine is a Calcium Ion channel blocker drug it specifically blocks the L type channels. It inhibits the calcium in flesh and the opening of the channel doors. It is orally absorbed up to 90% and has got its protein binding up to 92-98%. It is having its half-life up to 1.9 to 5.8 hours.

They have the bioavailability of 65% and are believed to be released in a sustained manner. They are peripheral vasodilators and have a depressants effect on SA and AV node. Reduced peripheral arterial Vascular Resistance and dilation of arteries leading to reduction in the systemic blood pressure and increased myocardial oxygen delivery.<sup>35</sup>

Nifedipine the prototype for the dihydropyridine group. Nifedipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle. The binding of nifedipine to voltage dependent and possibly receptor-oriented channels in vascular smooth muscle results in the inhibition of calcium influx through the channels.

This drug is also well tolerated by the pregnant patients as there are minimal disadvantages of this drug. It is believed that it doesn't cause much uterine blood flow and is found less traces in the human milk.<sup>[36]</sup>

Its toxicity in overdose have contraindications of allergy to nifedipine, hypotension, hepatic dysfunction.

#### **Verapamil**

Verapamil is a class of medication called Calcium channel blockers. It works by relaxing the blood vessels so that the heart does not have to pump as hard. It also increases the supply of blood and oxygen to the heart and lows electrical activities in the heart to contract the heart rate. It has got an oral absorption of more than 90% with an oral bioavailability of 10 to 35%. It has been eliminated through the Kidneys and has the half-life of 2.8 to 6.3 its protein binding is also up to 83-92%.

Same action nifedipine it also increases myocardial oxygen deliveries which help patients with vasospastic angina, where a record less with negative chronotropic effect with a decrease in sympathetic nervous system activity.

They are given as the second line treatment for Hypertension in pregnancy. They do not cause any teratogenicity and having good efficacy towards the treatment. They are the Calcium channel blockers and do not allow the influx of calcium to the vascular smooth muscle. They are given in the first trimester of pregnancy and have been found safe for breastfeeding also as very less amount or concentration of drug has been found in that milk.

They are also used to treat the fetal supraventricular tachycardia. It is usually well tolerated but its overdose can lead to negative inotropic and chronotropic effect and dilatation of artery and vascular and can also cause hypotension.<sup>37</sup>



### Furosemide

Furosemide is a loop diuretics medication used to treat fluid build-up due to heart failure, liver scarring and kidney disease. It may also be used for the treatment of high blood pressure. It has got an oral bioavailability of 60-64 % and has got the half-life of 6 hours. The onset of action for this drug is within 30 minutes.

Furosemide is an anthranilic acid derivative which acts rapidly and is a high efficacious diuretic. Its mechanism of action is by inhibiting the Sodium-Potassium-2 chloride co-transporter located in the thick ascending loop of Henle in the renal tubule junction.

Furosemide is given in the severe pre-eclampsia conditions. In pregnancy clearance is given to treat pulmonary oedema, fever, hypertension, in the presence of chronic kidney disease and constructive heart failure. It can lead to the decline of uteroplacental circulations which can cause harm to the foetus.

Side effects of the drug can be diarrhea, constipation, Vertigo, headache etc. It has got some serious. Few other more disadvantages are excess loss of water and electrolyte low level of thyroid hormones pancreatitis, liver damage, hearing loss etc.<sup>38</sup>

### Hydrochlorothiazide

Hydrochlorothiazide is characterized as long duration of action in terms of comparative minimal effective diuretic doses with chlorothiazide and also in terms of dose-

response effect. Hydrochlorothiazide was found to be less toxic than chlorothiazide.<sup>39</sup>

Hydrochlorothiazide has got its onset of action of two hours and it's well observed that the duration of the drug is 6 to 12 hours and it is not well metabolised. It has got its protein binding 40-68% and has got the elimination Half-Life of 10 to 12 hours. It has been excreted in the form of unchanged drug via urine.<sup>[40]</sup>

Hydrochlorothiazide acts on the distal convoluted tubules and inhibits the sodium chloride cotransporter system thus lowering the blood pressure. Toxicity of this drugs are hypokalaemia, hypochloraemia and hyponatremia.<sup>41</sup>

### Spirolactone

Spirolactone and its two metabolites bind to cytoplasm mineralocorticoid receptor and formation as aldosterone antagonist. This results in a Potassium sparing diuretics effects in the distal tubules of the kidney.

Spirolactone is class of mineralocorticoid receptor antagonist and it's a non-selective antagonist that can bind to androgen and progesterone receptors. And the mechanism of action is by binding at the distal tubule and collecting duct by decrease the is Sodium reabsorption and potassium secretion along with increased vascular stiffness and modelling and increased cardiac inflammation bridges remodelling. spironolactone works by competitively blocking aldosterone receptor mediated action.<sup>42</sup>

**Table 3:** Toxicity, category, oral absorption and half-life of the commonly used drugs

Drug Name	Category	Toxicity	Oral Absorption	Half life
<b>Labetalol</b>	Beta- blocker	Contraindicated in reactive airway disease, bradycardia, heart blocks and pulmonary edema.	30% to 40 %	6 hrs
<b>Atenolol</b>	Beta- blocker	Bradycardia, hypotension, low cardiac output, cardiac failure and cardiogenic shock	50% to 60%	6 hrs
<b>Timolol</b>	Beta- blocker	Dizziness, headache, shortness of breath, bradycardia.	90%	4 hrs
<b>Methyldopa</b>	Antihypertensive	Dry mouth, haemolyticanaemia, elevation of liver enzymes noted rarely. Contraindicated in known hypersensitivity and acute liver injury.	25%	2 hrs
<b>Verapamil</b>	Calcium-channel blockers	Cardiac conduction, depressed myocardial contractility and hypotension	10% to 35%	4 hrs
<b>Furosemide</b>	Diuretics	Dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalaemia and hyperchloremic alkalosis and are extension of its diuretic action.	60% to 65%	6 hrs
<b>Hydrochlorothiazide</b>	Diuretics	Hypokalaemia, Hyponatremia, and hypomagnesemia	65-75%	10 to 12 hrs
<b>Spirolactone</b>	Aldosterone receptor antagonists	Drowsiness, confusion, maculopapular, nausea, vomiting, dizziness and diarrhoea	73%	1 to 3 hrs
<b>Isosorbide Dinitrite</b>	Antianginal	Low blood pressure, dizziness, headache, nervousness	20% to 25%	6 to 7 hrs
<b>Hydralazine</b>	Vasodilators	Hypotension, tachycardia, headache, flushing, myocardial ischemia, myocardial infarction	26% to 50 %	3 to 7 hrs



Spironolactone increases Sodium and chloride Ion excretion along with reduction in potassium and excretion it also increases calcium excretion through direct action on tubular transport.

This drug has the bioavailability of 73% and the half-life of 1-3 hours. It is metabolized in the liver to active metabolites and is excreted via urine. Its protein binding is up to 90%.

It is preferable for Potassium retention. It is highly compatible for breastfeeding. It is mostly preferred to be prescribed in the first trimester of pregnancy one of the greatest drawbacks of this drug is that causes antiandrogenic effect to the fetal.<sup>43</sup>

There are the rare reports of spironolactone causing liver toxicity of black and magnificent as elevation in serum transferase and Alkaline phosphatase in hepatocellular makes platelet after one month of administration.<sup>44</sup>

### **Isosorbide Dinitrate**

Isosorbide dinitrate is an antianginal agent and vasodilator that relaxes vascular smooth muscle to prevent and manage hypertension causes. The pharmacological action is mediated by the active metabolite nitric oxide which is the lacs one isosorbide mono nitrate is metabolized.

The mechanism of action of isosorbide it is a night ride that exerts its pharmacological effects by release nitric oxide and endothelial that derived relaxing factor. The oral bioavailability of isosorbide dinitrate is up to 20 to 25% and is given in the form of oral or sublingual tablets for stop the onset of action for this drug is 15 to 10 minutes and the duration of action is up to 6 to 7 hours.

Isosorbide dinitrate is usually given to the pregnant patients suffering from gestational hypertension and preeclampsia. Overdose causes systemic hypertension heart block with bradycardia increased intracranial tension.<sup>45</sup>

### **Hydralazine**

Hydralazine is a direct vasodilator used orally to treat essential hypertension among the patients suffering from the diseases and is given intravenously to rapidly reduce blood pressure in hypertensive urgency or emergency. This drug has an onset of action of 5 to 15 minutes with the duration of one to five hours. It has got the half-life of 3-7 hours. Hydralazine is a direct arterial vasodilator optically with associated with intracellular calcium homeostasis. Specifically, it inhibits Inositol triphosphate induced release of Calcium from the smooth muscles sarcoplasmic reticulum and inhibits myosin phosphorylation within the arterial smooth muscle.

This drug is safe enough to be given in all the trimester but most probably it is preferred in the acute severe hypertension during the second and the third trimester of pregnancy. Hydrolysis is approved as the FDA Class C drugs and it is found to be used in the breast feeding as very less cases or negligible traces of this drug has been found in the

human milk. There are very few cases or incident where the hypotension is been seen as the side effect for this drug.<sup>46</sup>

### **Postpartum and Breast-Feeding**

#### **Postpartum hypertension**

Postpartum stage after or following childbirth. Almost 12% of patients suffer from Postpartum hypertension. In this the patient experience systolic as 150 mm HG and diastolic as 100 mm HG. These readings maintained for almost four to five days after the childbirth and is expected to normalize in the next three months. This type of hypertension usually arises due to gestational hypertension or preeclampsia. And even if the drugs of hypertension is continued after 3 months then it is necessary to get Consulted for chronic hypertension. The medicines for Postpartum hypertension are always given by keeping in mind breastfeeding. Because in many of the cases if the drug is transferred to the baby, it can affect the infant's plasma concentration.<sup>47-49</sup>

During pregnancy the use of nonsteroidal anti-inflammatory drugs like ibuprofen, Paracetamol, aspirin, etc. are also responsible for causing Postpartum hypertension. And henceforth, it is suggested to avoid it. Other reasons for Postpartum hypertension can be due to huge intake of fluids or the vascular tones getting restored to the pre-pregnancy levels.<sup>50, 51</sup>

#### **Breastfeeding**

It's a very Complex and unpredictable process of drug transfer via breastfeeding. We all know it's a type of excretion of the drug from a human body. Acidity, lipophilicity and protein binding of the drug contributes to its transfer in the milk.

Following are few of the predictable factors resulting in drug transfer through breastfeeding:

- Basic drugs
- Drugs with low molecular weight
- Drugs with more lipophilic solubility
- Drugs with less protein binding<sup>52,53</sup>

Basic drug tend to get transferred in the milk because the human milk is acidic in nature and basic drugs are more absorbed and solubilized in acidic environment. Drug with lower molecular weight anyways can pass through the barriers. Drugs with higher lipophilic solubility gets concentrated in the milk because the concentration of lipids is more in the milk than the plasma.<sup>54, 55</sup>

#### **The concept of m/p ratio**

This is the excretory property of the drug in the breast milk. M/P ratio is the formula with which are able to find or estimate the milk to plasma drug concentration. Here the formula M/P is the total maternal milk / maternal plasma drug concentration ratio. This ratio helps us to



estimate the amount of drug concentration in the suckling infant. With the help of this formula the minimum amount of drug concentration in the plasma for any adverse consequences can be estimated. In the neonates the ability to clear the drug from the body is weak in the initial period but as soon as the baby reaches the one month its drug clearance gets improved.

**Formula=M/P = total maternal milk/maternal plasma drug concentration**

The method to know the infant clearance of the drug can be estimated by three methods as follows:

- pKa Value
- plasma protein binding

- octanol/water partition coefficients.

The ratio also has its own spectrum for the results as follows:

- if M/P is more than 1 then it indicates concentration of the drug in the milk is more than that in the maternal plasma.
- If M/P is between 0.5 – 1.0 then it indicates that the equilibrium is been balanced between the milk and the maternal plasma.
- If the M/P is less than 0.5 then is too much restricted or limited.
- If the M/P is less than 0.1 then it is considered nil or negligible<sup>56-58</sup>

**Table 4:** A brief about commonly prescribed drugs for hypertension during lactation along with their M/P ratio.

Sr. No	Medication	Total sample Size	High M/P >1.0	Intermediate M/P 0.5-1.0	Low M/P <0.5	Negligible M/P <0.1
1.	<b>Beta-blockers</b>					
	Metoprolol	23	21	1	1	-
	Sotalol	17	14	2	1	-
	Timolol	13	6	3	4	-
	Labetalol	3	2	1	-	-
	Propranolol	13	1	8	4	-
2.	<b>Ca<sup>2+</sup> channel blockers</b>					
	Diltiazem	1	1	-	-	-
	Verapamil	1	-	1	-	-
	Nitrendipine	4	1	2	1	-
	Nimodipine	5	1	1	3	-
	Nifedipine	2	-	-	2	-
3.	<b>Methyldopa</b>					
	Methyldopa	8	-	2	5	1
4.	<b>ACE inhibitors</b>					
	Enalapril	9	-	-	1	8
	Captopril	11	-	-	-	11

**CONCLUSION**

Getting a real idea and a concrete support on this topic is quite a tedious job. Focusing on the little facts that, it is concluded that chronic hypertension, gestational hypertension and preeclampsia are the most common type of hypertension that is affecting the pregnant women population. Up to 10% of pregnant population suffers from hypertension. All the commonly occurring hypertension in pregnant women is scaled up to 150 -160 mmHg systolic and 100-110 mmHg diastolic. The most customary prescribed drugs for the management of high BP are the first line treatment which are Labetalol, Methyl-dopa and Nifedipine. Since these drugs are used as the first line of treatment, they exhibit very few adverse drug effects. Therapeutic drugs like Atenolol which are used even in the pre-existing hypertension that might have taken place

before pregnancy. Such drugs also exhibit appreciable treatment. When we come to Postpartum and breastfeeding activity, we need to be more careful with the selection of the drug as there are maximum chances of the drug passing from the mother to the Infant and this may lead to several defects in the Infant. As the study or the evaluation of the excretion of drug in the milk is very difficult in many ways. In this topic also we little strong evidence. But still the researchers have come up for the safety and the concept of M/P ratio is being calculated of each and every drug in use. Even here for the breastfeeding mother's methyldopa, verapamil, enalapril are highly recommended for the treatment.

Even after all the requisite precautions are these exquisite medications reliable for a long time with respect to their safety towards maternal and the fetal?



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