WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Cardiovascular Drugs in Pregnancy

[1]Miss. Akanksha Adhik Panwal, [2]Mr. Khan. Z. K.

[1]Student, LNBCIOP, Satara
[2]Principal, LNBCIOP, Satara

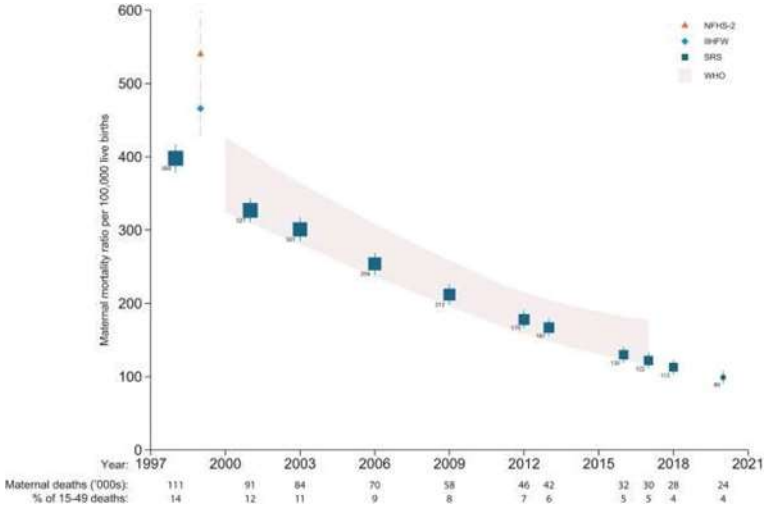
ABSTRACT:

Cardiac disease in pregnant women is most commonly due to rheumatic heart disease (RHD), congestive heart failure, and less commonly due to ischemic heart disease or cardiomyopathy. Though the frequency of RHD has decreased worldwide, it is still predominant in developing countries such as India. Around 15 to 52% of cardiac abnormalities first diagnosed during routine antenatal checkups or due to the signs and symptoms caused by physiologic changes of pregnancy. The most common clinical features of cardiac lesions such as breathlessness, pedal edema, and murmurs that mimic normal physiologic changes in pregnancy pose a diagnostic difficulty for obstetricians. Heart failure medications, including beta-blockers, furosemide, and digoxin, are relatively safe and can be used effectively. Medications that block the renin angiotensin–aldosterone system have been shown to be beneficial in the general population; however, they are teratogenic and, therefore, contraindicated in pregnancy. Cardiovascular medications can also enter breast milk and, therefore, care must be taken when selecting drugs during the lactation period. Significant physiological changes during pregnancy affect the heart's ability to respond to pathological pro- cesses such as hypertension and heart failure. These physiological changes further affect the pharmacokinetic and pharmacodynamic properties of cardiac medications. During pregnancy, these changes can significantly alter medication efficacy and metabolism. This article systematically reviews the literature on safety, efficacy, pharmacokinetics, and pharmacodynamics of cardiovascular drugs used for Cardiac disease during pregnancy and lactation.

Keywords: pregnancy, hypertension, heart failure, cardiovascular, medications

INTRODUCTION:

The incidence of pregnancy-associated cardiac problems in India is 1 to 4%. The most common etiology for heart diseases in pregnancy is rheumatic heart disease (RHD), congestive heart failure (CHF), and ischemic heart disease or cardiomyopathy. Though the frequency of RHD has decreased worldwide, RHD is still predominant in developing countries such as India. Around 15 to 52% of cardiac abnormalities first diagnosed during routine antenatal checkups or due to the signs and symptoms caused by physiologic changes of pregnancy. The most common clinical features of cardiac lesions such as breathlessness, pedal edema, and murmurs that mimic normal physiologic changes in pregnancy pose a diagnostic difficulty for obstetricians. In the western world, there was a steady increase in maternal mortality, reportedly due to heart problems from 1999 to 2014.Raised hemodynamic burden in pregnancy is an established fact. Hence complication rate may be greater in this population. One-third of women with heart disease use medication for the treatment of cardiovascular disease (CVD) during pregnancy. Increased plasma volume, renal clearance, and liver enzyme activity in pregnant women change the pharmacokinetics of these drugs, often resulting in the need for an increased dose. Fetal well-being is a major concern among pregnant women. Fortunately, many drugs used to treat CVD can be used safely during pregnancy, with the exception of high-dose warfarin in the first trimester,



Angiotensin-converting-enzyme in hibitors, angiotensin-receptor blockers, amiodarone, and spironolactone. A timely and thorough discussion between the cardiologist and the pregnant patient about the potential benefits and adverse effects of medication for CVD is important. Noncompliance with necessary treatment for cardiovascular disorders endangers not only the mother, but also the fetus. This Review is an overview of the pharmacokinetic changes in medications for CVD during pregnancy and the safety of these drugs for the fetus. The implications for maternal treatment are discussed. The Review also includes a short section on the cardiovascular effects of medication used for obstetric indications trends in maternal mortality ratio (MMR) from 1998 to 2018 and projection for 2020 for India. Each year on the horizontal axis represents the last of each three-year group for each MMR, except for 1998, which represents the second of two years. The pink bands represent the United Nations (UN)/World Health Organization (WHO) estimates. NFHS-2 is the National Family Health Survey, 2nd round, and IIHFW is the Indian Institute of Health and Family Welfare survey. Absolute maternal deaths are scaled to the UN demographic totals for females at 15–49 years of age.

The MMR declined in India by about 70% from 398/100 000 live births (95% CI 378–417) in 1997–98 to 99/100 000 (90–108) in 2020. About 1.30 million (95% CI 1.26–1.35 million) maternal deaths occurred between 1997 and 2020, with about 23 800 (95% CI 21 700–26 000) in 2020, with most occurring in poorer states (63%) and among women aged 20–29 years (58%). The MMRs for Assam (215), Uttar Pradesh/Uttarakhand (192) and Madhya Pradesh/Chhattisgarh (170) were highest, surpassing India's 2016–2018 estimate of 113 (95% CI 103–123). After adjustment for education and other variables, the risks of maternal death were highest in rural and tribal areas of north-eastern and northern states. The leading causes of maternal death were obstetric haemorrhage (47%; higher in poorer states), pregnancy-related infection (12%) and hypertensive disorders of pregnancy (7%).

Physiological Changes in Pregnancy:

Critical physiologic variations occur in several systems: cardiovascular, pulmonary, renal, gastrointestinal, and endocrine systems. These variations may cause a change in pharmacokinetics and bioavailability of drugs influencing the mother and foetus.

Absorption :

Is affected by reduced gastric motility. Because of this, drugs will reside in the stomach for longer period. There will also be decreased acid secretion and increased alkaline mucus production, which can influence the gastric pH and indirectly degree of ionisation and solubility of drugs.

Distribution:

There will be increase in plasma volume, total body water, and fat. Total albumin is reduced steadily during pregnancy. More amount of free drug is available because of decrease in binding protein (albumin).

Metabolism:

Several enzymes in the placenta metabolise the drugs. The foetus takes active part in metabolism after 6 to 8 weeks of pregnancy.

Excretion:

Renal vascular perfusion and glomerular filtration rate will be increased significantly. Hence drugs primarily excreted by the kidney.

Hemodynamic Changes in Pregnancy :

Metabolic demands are increased in pregnancy. To compensate these demands, several changes occur in cardiovascular system. These changes are elevated blood volume and cardiac output (CO) and a decrease in systemic vascular resistance and blood pressure (BP). An increase of 40% in plasma volume occurs at 24 weeks.

Hence drug dosage should be increased to attain therapeutic concentrations of the drugs. During the entire pregnancy, up to 30 to 50% of elevation occurs in CO. A rise in heart rate occurs at 20 weeks and is maintained until 2 to 5 days post-delivery. The size of heart may become larger up to 30%.

Pharmacokinetic and Pharmacodynamic Changes in Pregnancy:

Pharmacokinetic properties vary in pregnancy due to multiple physiological changes to cardiac, renal, and hepatic function and body fat distribution. Decreased gastrointestinal motility slows absorption and increases time to onset of action of oral medications. Decreased gastric acid variably affects medication dissolution and absorption depending on formulation. Increases in plasma volume and body fat lead to larger volumes of distribution, causing decreased steady- state concentrations of many medications. Serum albumin and alpha acid glycoprotein increase in pregnancy due to direct oestrogen effects on the liver, resulting in increased protein binding of most drugs and reduced free drug concentrations. Further hormonal influences on liver increase or decrease metabolism of some drugs without clear patterns. Finally, medications primarily excreted by kidneys have increased clearance rates due to the 25% increase in glomerular filtration rate (GFR) during pregnancy. Although many medications are not studied in pregnancy, a common misconception is that overall mechanisms of action remain unchanged. The dynamic physiological changes of pregnancy clearly affect the pharmacokinetic processes. In addition, hormonally induced alterations in receptor and transport expression may affect drug activity at receptor sites. Overall, pregnancy introduces unpredictability to the body's handling of medications.

Sr No	Condition	Drugs of choice
1.	Hypertension	Intravenous nifedipine labetalol or oral methyldopa or
2.	Arrhythmias	
	Supraventricular tachycardias (SVT)	
	Acute paroxysmal SVT	Intravenous (IV) adenosine or IV metoprolol or IV verapamil
	Chronic SVT	Oral digoxin or β–blockers – metoprolol or propranolol Second–line drugs: sotalol or flecainide, or propafenone
	Atrial fibrillation	β–Blockers, low–molecular– weight heparin (LMWH) or vitamin K antagonists
	Ventricular tachycardias	
	Acute VT hemodynamics with stable	IV sotalol or procainamide
	Acute VT with unstable hemodynamics	IV amiodarone
	Congenital long QT syndrome	β–Blockers
	Idiopathic sustained VT	Oral β–blockers: metoprolol/ propranolol or verapamil Second–line drugs: oral sotalol, flecainide, propafenone
3.	Heart failure	β–Blockers: hydralazine and nitrates instead of angiotensin–converting enzyme (ACE) inhibitors
4.	Pulmonary edema	IV nitroglycerine, diuretics: furosemide and hydrochlorothiazide
5.	Venous thromboembolism	LMWH
6.	Infective endocarditis	Penicillin, ampicillin, amoxicillin, erythromycin, mezlocillin, and cephalosporin
7.	Angina	β–Blockers, nitrates
8.	Myocardial infarction	IV nitroglycerine, unfractionated heparin (UFH)/LMWH

Hypertension :

The most common cardiac problem encountered in 10% pregnancies is hypertension (HTN). Affected women are also at increased risk for cardiovascular disease later in life, independently of traditional cardiovascular disease risks.

BP category	SBP	DBP
Normal	<120 mmHg	<80 mmHg
Elevated	120-129 mmHg	<80 mmHg
Hypertension		
Stage 1	130-139 mmHg	80-89 mmHg
Stage 2	140 mmHg	90 mmHg

Table: Categories of blood pressure in adults

Hypertensive disorders of pregnancy include chronic (pre- existing hypertension), gestational, pre-eclampsia, chronic hypertension with superimposed pre-eclampsia, eclampsia, and postpartum hypertension. Placental abruption (1.5%), foetal growth restriction (16%), and preterm delivery (34%) occur more commonly in chronically hypertensive pregnant women. When systolic pressure exceeds 180 mmHg or diastolic exceeds 110 mmHg, risk of complications more than doubles. Hypertension is also the strongest predictor for postpartum stroke within 48 hours post delivery. Data remain insufficient to determine optimal blood pressure (BP) for improved maternal/foetal outcomes. Thus, clear consensus is lacking on continuing or discontinuing therapy in women already on antihypertensives with mildly elevated BP. In patients not currently on medication, it is usually not re- commended to initiate

therapy until BP >160/110 mmHg.26 Gestational hypertension complicates *11% of first pregnancies and up to 7% of all pregnancies.27,28 Development of gestational hypertension during pregnancy increases the risk of hypertensive disorders in subsequent pregnancies and later in life.

Severity of HTN	**Treatment**
Mild HTN	Methyldopa, α–β–blocker labetalol Second–line drugs: calcium channel blockers—oral nifedipine
Acute–onset, severe HTN	Intravenous (IV) labetalol, IV hydralazine, or immediate release oral nifedipine
Hypertensive emergency	IV sodium nitroprusside, IV nitroglycerine

Table : Drugs for hypertension (HTN)

The initial choice of drugs is methyldopa, α-/β-blocker labetalol. Calcium channel blockers such as nifedipine (oral) or isradipine (IV) are second-line drugs. Long-term (> 30 years) data are available about methyldopa use in pregnancy, with the child's follow-up period of > 7.5 years. The decision of drug choice and route of administration depends on the expected time of delivery. In a pregnant woman, hypertensive emergency is defined as systolic BP (SBP) ≥170 or diastolic BP (DBP)

≥110 mm Hg. Sodium nitroprusside is the choice of drug in hypertensive emergency, which is given as an intravenous (IV) infusion at 0.25 to 5.0 mg/kg/min. This drug may cause foetal cyanide poisoning after prolonged treatment. In hypertensive emergencies, urapidil can also be considered. The drug of choice for pulmonary edema due to preeclampsia is nitroglycerine (glyceryl trinitrate) that should be given as an IV.

Heart failure:

Heart failure is a significant cause of maternal and foetal morbidity and mortality in pregnancy. Heart failure can be difficult to diagnose during pregnancy as symptoms such as fatigue, dyspnea on exertion, and bilateral lower extremity edema may also occur with normal changes of pregnancy. Antihypertensive drugs should be given for lowering the afterload along with bedrest and fluid and salt restriction. β-Blockers are advised for all pregnant women with heart failure. Metoprolol is the preferred drug. Atenolol is contraindicated. Newborns must be kept under observation post-delivery for 24 to 48 hours to rule out hypoglycemia, bradycardia, and respiratory depression. Foetal toxicity is reported with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and renin inhibitors. These drugs are contraindicated in pregnancy. Nitrates and hydralazine may be used in their place. Nitroglycerine can be given, for acutely ill patients admitted to intensive care unit (ICU), which is an arterial and venous vasodilator. The commonly administered inotropic agents are dopamine and levosimendan. Diuretics are the treatment of choice, if the pulmonary edema is due to increased preload because of pregnancy induced hyperdynamic circulation. Diuretics are not useful, if pulmonary edema is due to ventricular dysfunction. The commonly used diuretics are furosemide and hydrochlorothiazide. Aldosterone antagonists are contraindicated in pregnancy. Spironolactone may cause antiandrogenic effects in the foetus. No data are available for eplerenone. Hence it cannot be given in pregnancy

Guide to cardiovascular medication use during pregnancy and breastfeeding :

Drugs with high molecular weight, low lipid solubility, high protein binding, large volume of distribution, and short half-lives are preferred for the lowest transfer into breast milk. Selecting drugs with several of these characteristics should offer a lower risk to the breastfed infant. In one patient who was 14 days postpartum, peak milk levels of 190–230 lg/L occurred about 2 hours after the dose during an oral regimen of 60 mg four times daily. The levels and time course of the drug in milk closely paralleled serum levels. Using the peak milk level data from this patient, an exclusively breastfed infant would receive an estimated maximum of 0.9% of the maternal weight-adjusted dosage. although most events occurred during initiation of the med- ication. Labetalol has not been shown to have mortality benefits in heart failure compared with these beta-blockers. ACE-Is and ARBs are important medications in heart failure treatment in nonpregnant populations. However, as with hypertension, they should be avoided during pregnancy due to teratogenic effects such as malformation of the cardiovascular and neurogenic systems during the first trimes- ter. Hydralazine is often a second-line agent for afterload reduction in the nonpregnant state. Given that the physiology in pregnancy naturally reduces systemic vascular resistance, this additional afterload reduction is often not needed. Regarding diuretics, a study of pregnant women with de- creased cardiac output and increased BP showed furosemide reduced SBP and DBP while maintaining heart rate (p = 0.002). However, the study was not adequately powered to determine maternal and foetal outcomes. Therefore, caution remains regarding its use in pregnancy due to the possibility of foetal growth restriction and hypokalemia. Furosemide can be used sparingly for symptoms of volume overload. As aldosterone antagonists have been shown to cause feminization of developing male rats, there is concern surrounding the antiandrogenic effects of spironolactone during the first trimester. Thus, all aldosterone antagonists should be discontinued during pregnancy (pregnancy class D). Digoxin is a pregnancy class-C sodium/potassium ATPase inhibitor and direct suppressor of atrioventricular nodal conduction. It crosses theplacenta readily during later pregnancy, but no adverse effects have been observed to the mother or foetus. Digoxin is generally used in pregnant women with persistent heart failure symptoms on beta- blockers, nitrate/hydralazine, and diuretic therapy.

Potential Role of Precision Medicine and Pharmacogenomics in Pregnancy :

Patients with hypertension and preeclampsia may remain nonresponsive to antihypertensive therapy. Precision medicine and pharmacogenomics may help guide personalised treatment for patients throughout their pregnancy. Cytochrome P450 (CYP) 2D6 [CYP2D6] is involved in the metabolism of 25% of commonly prescribed medications and has shown increased activity in pregnancy; pregnancy may be the only known cause of increased CYP2D6 activity. Some patients may experience little or no effect from medications, particularly metoprolol (metabolised by CYP2D6), if they are ultra-metabolizers. Cytochrome P450 (3A) [CYP3A] metabolises other medications routinely used among pregnant patients, such as calcium-channel blockers (nifedipine). A study by Tracy et al. assessed temporal changes in drug metabolism during pregnancy and found that CYP3A activity was consistently elevated (35%–38%) during all pregnancy stages. Thus, knowing patients' genotype before starting therapy could lead to medication choices best suited for the patient. However, DNA isolation, assays/analysis, and cost of testing currently make this concept impractical.

Conclusion :

The cardiac problems that require therapy should be treated with drugs that have enough evidence for safety and efficacy of their use. Treatment should be given only when indicated, after careful risk-benefit assessment of both the mother and foetus. Risk-benefit ratio of drugs to be used in pregnant women must be established using various resources.

High-risk pregnant patients with cardiovascular disease require multispecialty teams from obstetrics and gynaecology, maternal foetal medicine, internal medicine, cardiovascular disease, and pharmacology. Successful man- agement of these complex patients increases favourable out- comes, whereas minimising postpartum morbidity and optimising maternal disease status, allowing for future un- complicated pregnancies. Certain cardiovascular medications are safe during pregnancy, mitigating the rise in maternal mortality, and they play an important role in management of high-risk patients.