Cardiac Drugs in Pregnancy

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Abstract

Heart disease complicating pregnancy is an indirect cause of maternal mortality and its incidence in India is 1 to 4%. 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.

Keywords
- cardiac drugs
- cardiac drugs in pregnancy
- pregnancy

Introduction

The incidence of pregnancy-associated cardiac problems in India is 1 to 4%.[1]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.[2,3]

In the western world, there was a steady increase in maternal mortality, reportedly due to heart problems from 1999 to 2014.[4,5] Raised hemodynamic burden in pregnancy is an established fact. Hence complication rate may be greater in this population.[6]

Physiologic 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 fetus.

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 ionization 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 metabolize the drugs. The fetus 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 are increased.

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

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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%.[4]

Hemostatic Changes in Pregnancy

There will be a rise in the serum levels of platelets, coagulation factors, and fibrinogen and a decrease in fibrin degradation products. All these changes lead to a state of hypercoagulability that in turn leads to risk of thromboembolic events.

Metabolic Changes

Serum cholesterol levels are elevated according to demand. Blood glucose levels may increase in susceptible persons.

Genetic Testing and Counseling

The risk of transmitting the heart disease is higher if the mother has the disease, and it varies with the type of cardiac disease the mother has. Autosomal dominant inheritance is more common than autosomal recessive and X-chromosomal recessive inheritance.[7] Genetic testing is helpful in cardiomyopathies and channelopathies. Other family members are affected when the patient has dysmorphic features, developmental delay/mental retardation, or when other noncardiac congenital abnormalities are present, in syndromes such as in 22q11 deletion, Marfan's, Williams-Beuren, Alagille's, Noonan's, and Holt-Oram syndromes.

Genetic counseling by a geneticist is essential for patients as well as their family members because type of inheritance varies depending on the cardiac disease. Genetic testing helps in the identification of asymptomatic relatives of the patients and forms a basis for clinical surveillance.[8] Genetic testing is indicated in pregnant women with known genetic disorders. Genetic screening is advocated by chorionic villous biopsy at 12th week and fetal echocardiography between 19th to 22nd weeks of pregnancy. The initial genetic screening test for the women older than 35 years is measurement of nuchal fold thickness at 12th to 13th weeks of pregnancy.[9]

In general, drugs will not be prescribed in pregnancy unless there is dire need. Risk-benefit ratio must be established if drugs should be prescribed. Drugs will be selected based on the clinical evidence of their toxicity in pregnancy and stage of the pregnancy. The pharmacokinetics of drugs is altered during gestation. Drug effects always may not be predicted; hence, intense clinical monitoring by laboratory methods is required.[10]

General Considerations when Prescribing in Pregnancy

Several pregnant women need drug prescription in pregnancy. To withdraw the treatment could be detrimental for the mother and fetus. Drug prescribing is challenging because of various reasons: (1) Physiologic variations occurring in pregnancy can affect drug bioavailability; (2) insufficient information regarding the side effects of new drugs; (3) whether to treat the patient is absolute necessary; and (4) using the available medical resources for the drug use.[11] While prescribing the drugs, the health care provider and the patient should confer, and the patient can be informed of the choices regarding the optimum treatment to minimize risks to her pregnancy. The lowest effective dose, for the shortest possible period, should be given. Drugs can act synergistically in terms of teratogenic potential. Hence monotherapy is advisable when possible. There are not enough studies of pregnancy outcome in relation to drug exposure. Only preclinical studies are available. Extrapolation of data from animal reproductive studies to humans is difficult because of species-to-species variation.

Several online databases review, summarize, and periodically update information from the peer-reviewed medical literature.[12–16] The REPRORISK system[13–16] maintained by Micromedex (Greenwood Village) provides access to several databases that contain information about a wide range of individual medications: REPROTEXT, REPROTOX, Shepard's Catalog of Teratogenic Agents,[16] and the Teratogen Information System (TERIS).[13] Online access and a smartphone "app" for these databases are available for a subscription fee. Summaries for individual medications can be ordered directly from TERIS, also for a fee.

Good Prescribing Practices in Pregnancy[11]

Optimal therapeutic benefit can be assured, if good prescribing practices are followed in pregnancy. They include the following:

- The patient must be included in decision making. Health care provider should identify her concerns, worries, and preferences in her illness and treatment.
- Information should be imparted to the patient, regarding the risk of not prescribing the treatment for the disease versus risk of giving the treatment.
- Drugs must be selected, which have long-standing evidence on safety and the patient should be informed of the resources used, for selecting the drug.
- It is mandatory to do a literature search, whenever the prescription is written for a pregnant patient.
- Health care provider should discuss with the patient and her family in the preconception period itself, if possible.
- Right drug has to be selected for right trimester.
- Treatment plan in pregnancy should be discussed with the patient.
- Criteria should be defined clearly, when to stop the treatment.

Cardiac problems in pregnancy require more experience and skill for managing them.[17] Understanding and knowledge of pharmacokinetic profile of drugs is essential for drug prescription in pregnancy.[18]

The pregnancy and lactation labeling (drugs) final rule (PLLR) was introduced by the Food and Drug Administration

(FDA) in 2015. Pregnancy categories—A, B, C, D, and X—are replaced by PLLR. PLLR provides information regarding the drug use in pregnancy and helps the health care providers estimate the risk versus benefit. The health care providers pass on this information to the pregnant patients and allow them to decide on which drug must be taken. PLLR will be updated when new information is available. The differences between previous labeling and PLLR are shown in ►**Table 1**.

Section 8.1 includes data for pregnancy exposure registry. These registries obtain and store information on the effects of approved drugs that are prescribed for pregnant patients. They consist of risk summary and clinical considerations. Previously drug registries are recommended, but they are mandatory now. Section 8.2 includes data of drug use in lactation and drug effects on breast-fed babies. The new Section 8.3 comprises data about pregnancy studies, infertility studies, and contraception recommendations relating to drugs.[19] The commonly used cardiac drugs are discussed in ►**Table 2**.

Antihypertensive Drugs

The most common cardiac problem encountered in 10% pregnancies is hypertension (HTN). The studies on pregnancy-induced hypertension did not show any benefit of treating mild to moderate cases. In 2013, the European Society of Cardiology (ESC) task force on HTN suggested that early therapy with antihypertensives should be started, if the BP is ≥140/90 mm Hg in cases of preexisting HTN or pregnancy-induced HTN or appearance of HTN in any time of pregnancy (►**Table 3**).[4,20] 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.[4,21] 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 fetal 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

Table 1 Drug labeling section—use in special populations

Previous labeling	New labeling (effective from June 30, 2015)
8.1 Pregnancy	8.1 Pregnancy: includes labor and delivery
8.2 Labor and delivery	8.2 Lactation: includes nursing mothers
8.3 Nursing mothers	8.3 Female and males of reproductive potential

Table 2 Commonly used cardiac drugs in pregnancy

S No.	Condition	Drugs of choice
1	Hypertension	Intravenous labetalol or oral methyldopa or nifedipine
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 (VT)	
	Acute VT with stable hemodynamics	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 cephalosporins
7	Angina	β–Blockers, nitrates
8	Myocardial infarction	IV nitroglycerine, unfractionated heparin (UFH)/LMWH, acetyl salicylic acid (ASA) < 100 mg/day

Table 3 Drugs for hypertension (HTN)

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

infusion of 5 mg/min, gradually increasing every 3 to 5 min up to a maximum dose of 100 mg/min. The preferred drug for seizures due to eclampsia is IV magnesium sulphate. The previous literature stated that there were no interactions with simultaneous administration of magnesium sulphate and nifedipine.[22] Diuretics are not recommended in preeclampsia because they reduce blood flow to the placenta. Many antihypertensive drugs, except propranolol and nifedipine, are secreted in breast milk in low concentrations.[4]

Antiarrhythmic Medications

The more common presentation of arrhythmias in pregnancy is ectopic beats and supraventricular tachycardia (SVT) type (20–44%). They may be benign but require investigations to exclude underlying structural heart disease. Treatment is individualized depending on the type of tachyarrhythmia. Vagal stimulation is the treatment of choice in acute SVT. If it is not successful, IV adenosine is the choice. Class I β-blockers and sotalol can be given carefully if left or right ventricular function impairment is present. Initially small doses should be started with monitoring of clinical condition of the mother and the fetus regularly. For all drug refractory arrhythmias, electrocardioversion is the choice. Amiodarone is the treatment of choice when other drugs failed. Digoxin and selective β-blockers are the choice of drugs for prophylaxis.[23]

Class I antiarrhythmic drugs act by blocking the sodium channels. The studies with quinidine, procainamide, and lidocaine showed that they are relatively devoid of side effects during pregnancy. Quinidine has been used during pregnancy since 1930. Quinidine may cause fetal thrombocytopenia. Premature labor, abortion, or damage to the fetal eighth cranial nerve may occur with supra therapeutic doses of quinidine.[10] IV ibutilide or flecainide can be considered for atrial flutter with normal heart. However, limited data are available on their efficacy and safety in pregnancy. In drug-resistant cases, IV propafenone or the IV vernakalant (the new class III antiarrhythmic drug) can be considered.

The ventricular rate in atrial fibrillation (AF) can be controlled with β-blocking agents, digoxin. The serum concentrations of digoxin are unpredictable in pregnancy. AV nodal blocking drugs (digoxin, verapamil, and diltiazem) can be used as second-line drugs in this condition. Flecainide and propafenone must be given along with AV nodal blocking agents. A new drug dronedarone is contraindicated in pregnancy.

Class II drugs are contraindicated in the first trimester of pregnancy. Propranolol is the longest studied drug in pregnancy and has not been proven to be teratogenic. Data regarding metoprolol and atenolol use are still limited, but there are no proven side effects on the fetus. Pindolol can be more beneficial in pregnancy because it does not affect resting heart rate and CO. It does not diminish uterine blood flow and fetal heart rate due to its direct vasodilator property.[22,24]

In class III drugs, the potassium channel–blocking agent amiodarone is used for acute treatment of ventricular tachycardia (VT), if electrocardioversion fails. Amiodarone should be considered for treatment of resistant VT, and if necessary, also during pregnancy for protection of maternal life. It causes prematurity, growth retardation, fetal hypothyroidism, bradycardia, and QT prolongation. Considerable concentrations of amiodarone will be achieved in breast milk.

Cardiac glycosides have been well-established drugs since the ancient times. Digoxin is the most commonly used drug among all cardiac glycosides. It is used in pregnancy for the treatment of chronic heart failure and SVTs. The previous literature on digoxin did not establish any teratogenic effect in humans. However, higher doses are necessary in pregnancy to attain therapeutic concentrations.[10,23]

The incidence of bradyarrhythmias in pregnancy is infrequent and generally tolerated well. In small percentage of patients, pacemaker implantation is required. Ectopic beats are generally not harmful, and some of the healthy pregnant women also have these beats. Reassurance is the treatment of choice.[23,25]

Acute Coronary Ischemic Medications

Acute coronary syndrome (ACS) may present at any time during pregnancy. Incidence of ACS in pregnancy is 3 to 6 cases per 100,000 deliveries. Mortality due to ACS in pregnancy is 5 to 10% and is more common in peripartum period.[4,26] β-Blockers are the treatment of choice in all phases of ACS. The previous studies reported that nitrates can be given during pregnancy, and there were no reported side effects on feto-maternal unit. For a long time, nitroglycerine was administered in preterm labor.[22,27]

Statins are considered as potential teratogens, though they are widely used in pregnancy. The data regarding the use of statins in pregnancy are inconclusive. Studies on administration of statins in preeclampsia are being conducted on animals and humans.[28] Taguchi et al compared 64 pregnant women taking statins to controls and reported no difference in the incidence of congenital malformations in both the study groups.[29] However, statins may be given in high-risk cases in pregnancy, to reduce the risk, on case-to-case basis.

Anticoagulants

For women taking vitamin K antagonists, two options are available to reduce the risk of warfarin embryopathy. The first is to advise women to perform frequent pregnancy tests and substitute low-molecular-weight heparin (LMWH) for warfarin once pregnancy is achieved and before 6 weeks' gestation. Alternatively, LMWH or unfractionated heparin (UFH) can be substituted for vitamin K antagonists before conception is attempted.[30] Anticoagulants are required infrequently in pregnancy. The purpose of using these drugs is prophylactic—in preventing valve thrombosis and venous thromboembolism and in the treatment of myocardial infarction (MI). Increased risk of abortion and retroplacental bleeding leading to premature delivery and intrauterine death are associated with anticoagulation therapy. UFH and LMWH cannot cross the placental barrier. Replacement of oral anticoagulants (OACs) with heparins reduces the risk of abortion and embryopathy. In pregnant women who are on OACs, vaginal delivery is contraindicated due to risk of fetal intracranial bleeding. While using heparins (UFH, LMWH), it is important to monitor anti-Xa levels. This level should be

maintained > 0.6 IU/mL. The initial dose of enoxaparin is 1 mg/kg body weight and dalteparin is 100 IU/kg, given twice daily subcutaneously. Depending on the weight and anti-Xa levels, dose of LMWH should be adjusted.[4] UFH should be started 36 hours prior to labor or cesarean section and must be stopped 4 to 6 hours prior to anticipated labor. It should be reintroduced at 6 hours post-delivery, if there is no bleeding. Both UFH and LWMH are not secreted in breast milk. Insufficient data are available regarding fondaparinux and rivaroxaban. Hence these drugs are not recommended in pregnancy. Heparin-like action is seen with danaparoid, and no teratogenic effects were reported in animal studies. Hence this drug may be administered as an alternative to heparin.[31]

If warfarin therapy is essential, it should be avoided at least during the first trimester (because of teratogenicity) and from about 2 to 4 weeks before delivery to reduce risk of hemorrhagic complications. Thromboembolic complications are more common in women with mechanical heart valves. Treatment choices in these patients include continued warfarin therapy, especially if daily dose is ≤ 5 mg and international normalized ratio (INR) ≤ 5, or weight-based LMWH dosed twice daily. Use dabigatran, a direct thrombin inhibitor is contraindicated in pregnancy because of mechanical valve thrombosis.[32] Xa inhibitors (rivaroxaban, apixaban, edoxaban) are likely to cross the placenta, and their human reproductive risks are unknown. Hence they are not indicated in pregnancy.

Thrombolytic Agents

These agents must be prescribed to high-risk cases with shock. In a study, 200 pregnant patients were given streptokinase and, more recently, recombinant tissue plasminogen activator (rt-PA). They did not cross the placental barrier in significant quantities. In this study, abortions (6%) and premature labors (6%) were reported.[33] The loading dose of UFH must not be given, if thrombolysis is administered. The infusion rate should be 18 U/kg/h. Once the condition is stable, UFH should be replaced with LMWH for the rest of pregnancy. Thrombolytic therapy with rt-PA is reserved for life-threatening ACS, for which percutaneous coronary intervention (PCI) cannot be attempted.[34] It may cause subplacental bleeding.

Antiplatelet Medication

It has been shown that acetyl salicylic acid (ASA) in a dose of < 100 mg/day has no effect on fetus or bleeding risk to either the mother or fetus. There are insufficient data regarding the use of clopidogrel in pregnancy. Studies in animals reported no teratogenic effects.[35] Hence clopidogrel can be prescribed for high-risk cases. Data are absent regarding the use of glycoprotein IIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor. Hence the use of these drugs is contraindicated in pregnancy.[4]

Heart Failure Medications

The treatment of heart failure in nonpregnant women is not different from that in pregnant women. 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.[36] Fetal toxicity is reported with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and renin inhibitors.[37] 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 ionotropic 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.[38] Spironolactone may cause antiandrogenic effects in the fetus. No data are available for eplerenone. Hence it cannot be given in pregnancy.

Drugs in Infective Endocarditis

An estimated risk of infective endocarditis in pregnancy is 0.006% (1/100,000 pregnancies).[39] The most common predisposing causes of infective endocarditis include presence of prosthetic heart valves, history of previous infective endocarditis, and some variety of congenital heart diseases. Antibiotics are the treatment of choice. Penicillin, ampicillin, amoxicillin, erythromycin, mezlocillin, and cephalosporins can be prescribed in all stages of pregnancy.[40]

There are few clinical guidelines that can be classified as "strong" evidence regarding the use of cardiac drugs in pregnancy. There are huge gaps in the evidence-based research. Knowledge in these gaps forms the basis for the direction of future research and guidance of future therapy.

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 fetus. Risk-benefit ratio of drugs to be used in pregnant women must be established using various resources.

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