DRUGS IN OBSTETRICS & GYNECOLOGY

An Official Publication of

Department of Obstetrics & Gynecology
Maulana Azad Medical College (MAMC)

Ashok Kumar
Krishna Agarwal
Sudha Prasad
DRUGS IN
OBSTETRICS AND GYNECOLOGY

Editors
Ashok Kumar
MD PhD FAMS FICOG FICMCH
Director-Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Krishna Agarwal MS
Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Sudha Prasad MS
Director-Professor and Head
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

The Health Sciences Publisher
New Delhi | London | Philadelphia | Panama
Dedicated to

All patients who provide us
the opportunities to learn
Contributors

Anjali Tempe  
Director-Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Anju Bhalotra  
Professor  
Department of Anesthesiology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Ankita Pal  
Senior Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Annotha K Ravi  
Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Ashok Kumar  
Director-Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Ashwani Khanna  
State TB Officer  
Delhi, India

Asmita M Rathore  
Director-Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Asmita Patil  
Assistant Professor  
Department of Physiology  
All India Institute of Medical Sciences (AIIMS)  
New Delhi, India

Aswathy Kumaran  
FNB Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

B Nisha  
Specialist  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Bhoomika Tantuway  
Senior Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Bidisha Singha  
Specialist  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Binni Makkar  
Senior Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Chandan Dubey  
Assistant Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Chetna Arvind Sethi  
Specialist  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India
Deepika S Sharma
Resident
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Deepi Goswami
Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Devender Kumar
Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Gauri Gandhi
Director-Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Gunjan Bhatnagar
Senior Resident
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Komal Rastogi
Resident
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Krishna Agarwal
Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Latika Sahu
Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Madhavi M Gupta
Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Madhur Kumar
Resident
Department of Surgery
Government Medical College
Amritsar, Punjab, India

Meenoo S
Resident
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Mridul Daga
Director-Professor
Department of Medicine
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Nalini Bala
Medical Officer
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Poonam Kashyap
Specialist
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Poonam Sachdeva
Specialist
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Preeti Singh
Assistant Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India
Purnima Gupta  
Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Pushpa Mishra  
Senior Medical Officer  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Rachna Sharma  
Specialist  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Reena Rani  
Senior Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Renu Tanwar  
Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Reva Tripathi  
Director-Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Sangeeta Bhasin  
Chief Medical Officer  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Sangeeta Gupta  
Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Shailja Singh  
FNB Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Shailja Verma  
Senior Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Shakun Tyagi  
Assistant Professor  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Shweta Tahlan  
Senior Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Snigdha Pathak  
Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Sudha Prasad  
Director-Professor and Head  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Supriya Hajela  
Senior Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India

Swati Kumari  
Resident  
Department of Obstetrics and Gynecology  
Maulana Azad Medical College and  
Lok Nayak Jai Prakash Narayan Hospital  
New Delhi, India
Drugs in Obstetrics and Gynecology

Swati Priya
Senior Resident
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Tanvi Raj
Senior Resident
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Vaishali Paliwal
Resident
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

YM Mala
Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India
Drugs are the integral part of medicine. The rational use of drugs has saved enumerable lives, prevented epidemics and promoted health in general. Accessibility to essential medicines is an essential element of a health system. However, to accrue the optimum benefits, the drugs have to be used optimally—the right indication, right drug, right dose, right duration, minimal toxicity, and at the lowest cost, denoted as "rational drug therapy".

Unfortunately, despite knowing the benefits of rational drug therapy, irrationality in the use of drugs is rather rampant to the extent that it has been identified as a major public health problem. Apart from causing harm to the health of people, it is responsible for high cost of health care impoverishing people and communities. As per a recent estimate, over 53 million people get impoverished due to health care cost and cost of drugs constitutes a major part of it. Irrational use of antimicrobial drugs resulting in high level of antimicrobial resistance has almost pushed us to preantibiotics era.

The specialty of obstetrics and gynecology is different from other specialties of medicine in many different ways. A practitioner of this specialty has to have artistic skills of a surgeon as well as wisdom of a physician. Unfortunately, this does not happen in reality and we tend to falter on the very basic principles of pharmacotherapy. Despite being a physician for a significant part of our routines, we keep getting confused when confronted with names of drugs—new or old, as well as pharmacological terms associated with it. One of the reasons is the unavailability of a resource book that is concise yet provides optimum amount of details to help us make well-informed decisions about the use of drugs.

We have attempted to fill this void through this modest attempt. The book includes description of commonly used drugs in obstetrics and gynecology. In the beginning of a chapter, common-related drugs are given in a table for quick-reference followed by other required details in the text. There are a total of 35 chapters, each one being concise enough to be read over a short time. We have tried to maintain uniformity throughout the book to make it more predictable and easy to understand. Enough number of tables are provided on essential information. The section on antimicrobials provides optimum choice of antibiotics in different clinical conditions. A table has been provided on classification of commonly used antibiotics, which will help the reader in choosing the right agent in different situations.

We hope that the book would serve its purpose and help practicing physicians as well as postgraduate students to practice rational drug therapy in their day-to-day practice. It was a great learning experience for us to go through the nuances of the subject. Despite of observing due diligence, we are sure that there would be mistakes and errors, which we hope that the generous readers would overlook and provide us feedback for improvement in the future editions.

We thank the contributors for painstakingly compiling their chapters. Mr Jai Mohan deserves special thanks for coordinating with the contributors and the publisher. We also thank M/s Jaypee Brothers Medical Publishers, New Delhi, India, for bringing out this work wonderfully.

Ashok Kumar
Krishna Agarwal
Sudha Prasad
# Contents

## SECTION I Principles of Drug Therapy

1. Rational Drug Therapy  
   *Krishna Agarwal*  
   3

## SECTION II Emergency Drugs

2. Drugs Used in Medical Emergencies  
   *Shakun Tyagi, Swati Kumari*  
   15

## SECTION III Antimicrobials Used in Different Clinical Conditions

3. Antibiotic Classification  
   *Krishna Agarwal*  
   27

4. Antibiotic Prophylaxis in Obstetrics and Gynecology  
   *Preeti Singh*  
   33

5. Preterm Premature Rupture of Membranes and Chorioamnionitis  
   *Krishna Agarwal, Shailja Verma*  
   What Studies have to Say?  
   40  
   Antibiotic Treatment in PPROM and Chorioamnionitis  
   41

6. Puerperal Infection  
   *Poonam Kashyap*  
   43

7. Human Immunodeficiency Virus During Pregnancy  
   *YM Mala, Bhoomika Tantuway, Arushika Yedla*  
   Drugs for HIV Positive Pregnant Women  
   46

8. Pelvic Inflammatory Disease  
   *YM Mala, Bhoomika Tantuway*  
   Treatment for Pelvic Inflammatory Disease  
   52

9. Vaginitis/Vulvitis  
   *YM Mala, Bhoomika Tantuway*  
   Vaginal Discharge  
   54

10. Tuberculosis  
    *B Nisha, Ashwani Khanna*  
    Classification of Currently Used Antitubercular Drugs  
    62  
    Treatment of Tuberculosis  
    70  
    Antituberculosis Treatment and Contraception  
    72  
    DOTS and DOTS-Plus  
    72
11. Urinary Tract Infection
   
   Nalini Bala, Tanvi Raj, Krishna Agarwal

SECTION IV Drugs Used during Labor, Delivery and Puerperium

12. Labor Analgesia
    
    Sangeeta Bhasin, Reena Rani, Anju Bhalotra

13. Cervical Ripening Agents
    
    Krishna Agarwal, Swati Priya

14. Oxytocics
    
    Poonam Sachdeva, Binni Makkar

15. Galactagogues and Lactation Suppressants
    
    Nalini Bala, Tanvi Raj

16. Preterm Labor
    
    Reva Tripathi, Meenoo S

SECTION V Drugs Used in Medical Disorders of Pregnancy

17. Anemia
    
    Renu Tanwar, Ankita Pal

18. Hypertensive Disorders of Pregnancy
    
    Sangeeta Gupta

19. Diabetes in Pregnancy
    
    Asmita M Rathore, Shailja Singh

20. Cardiovascular Disorders of Pregnancy
    
    Latika Sahu, Vaishali Paliwal

21. Thyroid Disorders in Pregnancy
    
    Ashok Kumar, Gunjan Bhatnagar, Deepika S Sharma, Madhur Kumar

22. Gastrointestinal and Hepatic Disorders of Pregnancy
    
    Chetna Arvind Sethi

23. Respiratory Disorders
    
    Poonam Kashyap, Mridul Daga

   Asthma in Pregnancy  169; Pneumonias in Pregnancy  179
24. Neurological and Psychiatric Disorders of Pregnancy  
   Pushpa Mishra
   Headache 183; Seizure Disorders 185; Psychiatric Diseases 190

SECTION VI Family Planning Drugs

25. Medical Termination of Pregnancy  
   Rachna Sharma, Ojaswini Sharma

26. Newer Contraceptive Drugs  
   Chandan Dubey, Reena Rani

SECTION VII General Gynecology

27. Fibroid and Endometriosis  
   Bidisha Singha

28. Menstrual Disorders  
   Madhavi M Gupta, Purnima Gupta
   Adolescent 229; Reproductive Age Group 234

SECTION VIII Reproductive Endocrinology

29. Polycystic Ovary Syndrome, Hirsutism and Hyperprolactinemia  
   Anjali Tempe, Komal Rastogi
   Weight Reduction 247; Treatment of Menstrual Dysfunction 247
   Prevention of Metabolic Syndrome 250
   Treatment of Androgen-related Symptoms 253
   Other Drugs 257; Acne 258; Hyperprolactinemia 258
   Hypothalamic Disorders 258; Pituitary Disorders 258

30. Ovulation Induction Drugs  
   Sudha Prasad, Aswathy Kumaran, Supriya Hajela
   Ovulation Induction Drugs 265; The Future 274
   Ovulation Induction in ART Cycles 274

31. Postmenopausal Drug Therapy  
   Deepti Goswami
   Postmenopausal Hormone Therapy 276; Estrogens 277
   Progesterones 279; Tibolone 280
   Nonhormonal Drugs for Menopausal Symptoms 281
   Selective Serotonin Reuptake Inhibitors: Paroxetine 281
   Selective Norepinephrine Reuptake Inhibitors 282
   Gabapentin 282; Clonidine 283; Complementary/Alternative Medicines 283
   Medications to Prevent or Treat Osteoporosis 283
   Selective Estrogen Receptor Modulator 284; Teriparatide 284
SECTION IX Anticancer Drugs

32. Chemotherapy in Gynecological Cancers 289
   Gauri Gandhi, Shweta Tahlan, Snigdha Pathak
   Alkylating Agents 289; Alkylating-like Agents 289; Antitumor Antibiotics 289
   Antimetabolites 289; Plant Alkaloids 291
   Topoisomerase-1 Inhibitors 292; Complications and Side Effects of Chemotherapy 292
   Case Scenarios 295; Chemotherapy for Germ Cell Tumors 297
   Chemotherapy in Endometrial Cancers 298; Uterine Sarcoma 298
   Gestational Trophoblastic Neoplasia 298; Vulvar Cancer 299

SECTION X Miscellaneous

33. Fetal Therapy 303
   Krishna Agarwal, Anoosha K Ravi
   Cardiac Arrhythmias 303; Thyroid Disorders 305; Adrenal Disorders 306

34. Vaccines 308
   Devender Kumar, Asmita Patil

35. Analgesics 313
   Krishna Agarwal, Shailja Verma

Index 317
**FDA PREGNANCY DRUG CATEGORIES**

<table>
<thead>
<tr>
<th>FDA Category</th>
<th>Type of Studies Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities in any trimester of pregnancy</td>
</tr>
<tr>
<td>B</td>
<td>Well-controlled studies in animals have revealed no evidence of harm to the fetus</td>
</tr>
<tr>
<td>C</td>
<td>No animal studies or the one’s reported have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in pregnant women</td>
</tr>
<tr>
<td>D</td>
<td>Risk to the fetus demonstrated in well-controlled or observational studies in pregnant women, however, the benefits of therapy could outweigh the potential risk. Acceptable for use in a life-threatening situation only</td>
</tr>
<tr>
<td>X</td>
<td>Positive evidence of harm to the fetus seen in well-controlled or observational studies in both animals and pregnant women. The use of the drug is contraindicated in women who are or might become pregnant</td>
</tr>
<tr>
<td>N</td>
<td>Not classified by FDA</td>
</tr>
</tbody>
</table>

**LACTATION DRUG CATEGORIES**

<table>
<thead>
<tr>
<th>Category</th>
<th>Safety</th>
<th>Type of Studies Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Safest</td>
<td>Controlled studies in breastfeeding women have not shown any risk to the breastfeeding infant and possibility of harm is remote</td>
</tr>
<tr>
<td>L2</td>
<td>Safer</td>
<td>Drugs which have been studied in limited number of breastfeeding women without any increase in adverse effects in the breastfeeding infant</td>
</tr>
<tr>
<td>L3</td>
<td>Moderately safe</td>
<td>There are no controlled studies, but risk of untoward effects on breast-fed infant is possible OR Controlled studies show minimal nonlife-threatening adverse effects. These drugs are given when potential benefit outweighs potential risk to the mother</td>
</tr>
<tr>
<td>L4</td>
<td>Possibly hazardous</td>
<td>There is evidence of risk to the breastfed infant or to the breast milk production. But these drugs can be used in life-threatening situation and when safer drugs cannot be used</td>
</tr>
<tr>
<td>L5</td>
<td>Contraindicated</td>
<td>Human studies showed significant risk to the infant, the risk of using drug clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated during lactation</td>
</tr>
</tbody>
</table>
Cardiovascular Disorders of Pregnancy

Latika Sahu, Vaishali Paliwal

INTRODUCTION
Cardiovascular disorders (CVD) of varying severity complicate one percent of pregnancies and contribute significantly to maternal morbidity and mortality rates.¹ Rheumatic heart disease and congenital heart diseases are the common pre-existing conditions and hypertension is the most common acquired condition. The incidence of maternal CVD appears to be growing, due to increasing maternal age, cardiovascular risk factors (e.g. obesity) and lifespan of patients with congenital as well as rheumatic heart disease. Studies suggest that pregnancy-related mortality has also increased over the last several decades, with deaths attributable to CVD also increasing.² It is of vital importance to manage the patients with CVD during pregnancy and the associated complications. The management of these patients requires a multidisciplinary approach with the involvement of obstetrician, cardiologists, anesthesiologists who are experienced in caring for these patients.

Hemodynamic changes in pregnancy begin with 5–8 weeks of gestation, peak in the late second trimester and continue until delivery and these can have a profound effect on the underlying heart disease. The cardiac output, heart rate and left ventricular stroke volume increases and the systemic and pulmonary vascular resistance decreases. Cardiac decompensation coincides with this peak in patients with pre-existing cardiovascular disease. Pregnancy induces hypercoagulable state and most commonly in the peripartum period. Studies show that pregnant women are three to four times more likely to have arterial thromboembolism and four to five times more likely to have venous thromboembolism as compared with women who are not pregnant.³ The physiological changes of pregnancy can affect the pharmacokinetic properties of cardiovascular drugs in the mother. Motility in the GI tract decreased which may affect drug absorption. Acid secretion decreased and mucus production increased which increases gastric pH and may affect the degree of ionization and solubility of drugs. Increased metabolism of drugs in the gut wall, or more complete drug absorption leading to increased bioavailability may occur due to longer transit time through the GI tract. Drug transfer across the placenta and the pharmacokinetic properties of certain drugs may influence the rate of passage to the fetus and fetal drug concentrations. Some antiarrhythmic drugs can be administered to the mother (e.g. digoxin), and through placental transfer, can treat fetal tachyarrhythmias.

As soon as a cardiovascular disease patient becomes pregnant or newly diagnosed heart disease during pregnancy the type of
cardiovascular lesion should be confirmed, drugs dosage and schedule are to be modified based on patients risk status and NYHA class. In this chapter we are discussing the drugs used for valvular heart diseases, congenital heart diseases, pulmonary hypertension, cardiomyopathies, heart failure, anticoagulation for surgically corrected heart diseases during and before pregnancy, infective endocarditis prophylaxis and treatment of arrhythmias.

**Cardiovascular Drugs**

The commonly used cardiovascular drugs during pregnancy are listed in Table 20.1.

**Adenosine**

**Pharmacology:** This is a purine nucleoside that formed from breakdown of adenosine triphosphate (ATP) and occurred naturally.

**Mechanism of action:** Adenosine can bind to purinogenic receptors of vascular smooth muscle and causes vasodilatation. Adenosine binds to type 1(A1) receptors coupled to G1 proteins in cardiac tissue, which opens potassium channels and inhibits calcium channels and hyperpolarize the cells. At sinoatrial (SA) node adenosine decreases its rate by inhibiting the pacemaker current, which decreases the slope of phase 4 of the pacemaker action potential. At atrioventricular (AV) node it decreases conduction velocity by inhibition of calcium channel. It inhibits the release of norepinephrine by acting on sympathetic nerves. Due to its electrical effect it reduces heart rate and conduction velocity at AV node and decreasing action potential of atrium fibers.4

**Pharmacokinetics:** It has very short half-life of 10 seconds due to uptake into the RBCs. In the RBC, it is deaminated by adenosine deaminase into inosine then further breakdown to hypoxanthine, xanthine and uric acid. These products are excreted by kidneys. Adenosine kinase acted on adenosine and rephosphorylated it to AMP and maintain the adenine nucleotide pool in cells. Administration by rapid IV over 1–3 seconds.5

**Dosage:** 6–18 mg IV bolus.6 It can be repeated if required.

**Indications:** As antiarrhythmic drug used specially for paroxysmal supraventricular tachycardia (PSVT) due to its AV node suppression effect. For acute episode it is used as bolus IV injection or IV infusion.

**Adverse drug reaction:** Patients can have flushing and headache due to vasodilatation. It can cause rapid arterial hypotension and AV block which is reversible after stopping the adenosine infusion. It is contraindicated in pre-existing 2nd or 3rd degree heart block. It may cause bronchospasm and cough, precipitate in asthmatics.5,7 It is a FDA Category C drug.

**Beta-blockers: Metoprolol**

**Introduction:** Beta-blockers bind to beta-adrenoceptors located in cardiac nodal tissue, the conducting system, and contracting myocytes. The heart has both $\beta_1$ and $\beta_2$
adrenoceptors. The predominant receptor type in number and function is $\beta_1$, beta-blockers by competing for the binding site prevent the normal ligand (norepinephrine or epinephrine) from binding to the beta-adrenoceptor.

**Pharmacology:** It is a $\beta_1$ selective or cardioselective adrenergic receptor blocker but at higher plasma concentrations it also inhibits $\beta_2$ adrenoceptors in bronchial and vascular musculature.

**Mechanism of action:** It decreases contractility, relaxation rate and conduction velocity in heart. It decreases heart rate and cardiac output at rest. It reduces systolic blood pressure and heart rate upon exercise. It induces tachycardia induced by isoproterenol and reflex orthostatic tachycardia.

**Pharmacokinetics:** The oral bioavailability of immediate-release metoprolol is about 50% and the volume of distribution is 3.2–5.6 L/kg. About 10% of metoprolol bound to serum albumin. It crosses the placenta and blood-brain barrier. It is found in breast milk. It is metabolized by CYP2D6 in liver. The mean elimination half-life is 3–4 hours and it may be increased to 7–9 hours in poor CYP2D6 metabolizers. It is eliminated by kidney and excreted in urine. Mostly <5% of oral dose and <10% of intravenous dose are excreted as unchanged drug in the urine and approximately 95% of the dose can be recovered in urine.

**Indications:** Hypertension, AF rate control, SVT, heart failure, angina, myocardial infarction, arrhythmias, HCM, mitral stenosis, cardiomyopathy.

**Contraindications:** Sinus bradycardia, greater than first degree heart block, sick sinus syndrome and peripheral arterial circulatory disorders.

**Dosage:** Intravenous used in SVT, AF rate control 5 mg over 3–5 min × 3 doses, 1.25–5 mg/6 hr. Tablets of 25 mg are available, 25–100 mg 6 hrly. Half-life 3–8 hr. To be stored in 20–25°C. Start with 100 mg/day in single or divided doses with or immediately following meals. In hypertension the effect may take one week to manifest and increased dose up to 450 mg/day can be used.

**Adverse drug reaction:** CNS—Tiredness and dizziness occurs in 10% cases and depression in 5% cases. Other effects are mental confusion, short-term memory loss, headache and nightmare, insomnia. CVS—In 3% of cases shortness of breath and bradycardia occurred. It may cause in 1% cases, arterial insufficiency, palpitations, congestive heart failure, peripheral edema and hypotension. Respiratory—Broncho-spasm, wheezing and dyspnea seen in 1% cases. GI—Diarrhea seen in <5% cases, nausea, dry mouth, gastric pain, constipation reported in about 1% of cases. Hypersensitive reaction like pruritus or rash occurred in 5% cases.

**Drug interaction:** Reserpine (Catecholamine depleting drugs), calcium channel blockers may have additive effect. Digoxin potentiates the action and increases the risk of bradycardia. CYP2D6 enzyme inhibitors (antidepressants) may increase the plasma concentration of Metoprolol. Concomitant use of hydralazine may increase the concentrations of metoprolol by inhibiting presystemic metabolism of metoprolol. It potentiate the action of alpha blockers like alpha methyl dopa, vasoconstrictive action of ergot alkaloids.

**Precaution:** In geriatric patients due to less metabolism and in patients with hepatic or renal impairment caution should be taken. To be used with caution in diabetes patients using insulin.

**FDA category-C:** It is secreted in breast milk (<1 mg/L).

**Nitrates/Nitroglycerin**

In medical use it is commonly called as “glyceryl trinitrite” or “GTN”. Used for the treatment of angina and heart failure.

**Pharmacology:** The GTN is a prodrug which must first be denitrated to produce the active metabolite nitric oxide (NO).

**Mechanism of action:** Nitrates produce NO by either reacting with sulfhydryl group or with enzymes like glutathione S-transferases, cytochrome P450 (CYP), and xanthine oxidoreductase. NO is a potent activator
of guanyl cyclase by heme-dependent mechanisms leading to cGMP formation which activates myosin light chain phosphatase.

**Pharmacokinetics:** Bioavailability <1%. Metabolized in liver, RBC and vascular wall. Half-life of GTN is 3 minutes. GTN is excreted in urine and bile. Duration of action in sublingual and spray route is 10 minutes. Transdermal patches 8–12 hr during intermittent therapy.

**Dosage:** Route of administration—Sublingual, spray, ointment, oral, IV, transdermal. Available in strength—0.2 mg/hr to 0.8 mg/hr NTG patches (transdermal). Sublingual tablets 0.3–0.6 mg up to 1.5 mg, spray 0.4 mg, ointment 2% 6 x 6 in, 15 x 15 cm, 7.5–40 mg. Effect lasts up to 7 hr. Oral sustained release 2.5–13 mg, duration of effect 4–8 hour. Intravenous 5–200 mcg/min, duration of effect 7–8 hour. 

**Adverse drug reaction:** Severe headache, severe hypotension, brady cardi a. Together with sildenafil may cause severe hypotension, circulatory collapse and death. It is a FDA pregnancy category C drug.

**Digoxin**

**Introduction:** It is extracted from foxglove plant *Digitalis lanata.* This is mainly used for atrial fibrillation/flutter and heart failure.

**Pharmacology:** Digoxin is a purified cardiac glycoside.

**Mechanism of action:** It has ionotropic action and neurohormonal effects. It inhibits Na-K-ATPase and activate the Na+–Ca2+ membrane exchange pump and thereby increases myocardial contractility. Neurohormonal effects mediated by improved circulation which increases vagal tone and decreases sympathetic tone. This leads to prolonged refractory period and slowing of conduction through the atrioventricular node and thereby slowing the ventricular rate. At lower serum digoxin levels neurohormonal effects are present and ionotropic effects are present at higher digoxin serum levels. Neurohormonal effects are the primary mechanism for the therapeutic actions in both heart failure and atrial fibrillation and ionotropic effects are less important for therapeutic effects of digoxin. This increases cardiac output in a hypodynamic heart without increasing oxygen consumption. It has no prominent effect on the blood pressure and can be used safely in hypertensives. It has diuretic effect also and helps in gradual excretion of salt and water.

**Pharmacokinetics:** Digoxin is usually given by oral route and intravenous route is also used in emergency. Half-life is about 36 hours in normal renal function and the dose is once daily 125–250 µg. The half-life is longer in patients with decreased renal function, and dose should be reduced or change to other glycoside like digitoxin which has much longer elimination half-life (around 7 days). Excretion by kidney and involves P-glycoprotein which leads to significant clinical interactions with other drugs used in heart failure like spironolactone, verapamil and amiodarone.

**Dosage**

**Oral:** 0.125–0.5 mg/day, half-life 38–48 hour, IV 0.25 mg every 2 hr until 2 mg total maintenance 0.125–0.25 mg/day used in AF/AFL rate control. Recommended effective plasma level for heart failure is 0.5–1.0 ng/mL and for atrial fibrillation is 1.0–2.0 ng/mL.

**Adverse drug reaction:** Common adverse drug reactions include gastrointestinal symptoms like nausea, vomiting, anorexia, neurological symptoms like weakness, fatigue, confusion and cardiac symptoms like supraventricular/ventricular arrhythmias, first, second or third degree heart block, sinus bradycardia, etc. Rare adverse drug reactions like visual disturbances and cardiac arrhythmias are dose dependent. Some medical conditions like dehydration, renal impairment, unstable heart failure, hypokalemia-over diuresis, hypothyroidism, myocardial infarction, hypercalcemia can increase the risk of digoxin toxicity either due to increased digoxin concentration or sensitivity to digoxin.

If any toxicity develop the digoxin dose to be reduced or stopped temporarily depending
on severity of symptom and symptomatic treatment of toxicity symptoms to be done.

**Drug interaction:** Quinidine, verapamil and amiodarone increases plasma levels of digoxin by displacing tissue binding sites and decreasing renal clearance. When used along with diuretics, it can cause increased K+ depletion resulting in tachyarrhythmias.

It is a FDA Category C drug.

**Diuretics**

**Furosemide**

**Introduction:** The commonly used diuretics in cardiovascular disorder is Furosemide which is a loop diuretic.

**Pharmacology:** It acts in ascending limb of loop of Henle in kidney where it inhibits Na+–K+–2Cl– cotransport which causes a significant fraction of sodium reabsorption. So it causes increased loss of water, sodium, and potassium electrolytes.

**Mechanism of cardiovascular effects:** It effects on sodium and water balance, decreases blood volume and venous pressure leading to decrease in cardiac preload which is followed by decrease in ventricular stroke volume and cardiac output and then leads to a fall in arterial pressure. It causes venodilatation which leads to lowering of venous pressure followed by reduction of capillary fluid filtration and promotes capillary fluid reabsorption and thereby reduces edema. On long-term use it results in decrease systemic vascular resistance that helps to sustain the reduction in arterial pressure. Due to its action on renal prostaglandin synthesis it causes increase in renal blood flow and redistribution of renal cortical blood flow there by increases GFR and helps in quick relief of LVF and pulmonary edema.

**Pharmacokinetics:** The onset of action is 2–5 minutes in intravenous route, 10–20 minutes in intramuscular route and 20–40 minutes in oral route. It is rapidly absorbed but the bioavailability is 60%. In severe CHF, bioavailability may be markedly reduced necessitating IV administration. The duration of action lasts for 4–6 hours. It is highly bound to plasma proteins and partly conjugated with glucuronic acid and mainly excreted by glomerular filtration as well as tubular secretion in kidney. Plasma half-life averages 1–2 hours but is prolonged in pulmonary edema, renal and hepatic insufficiency.

**Therapeutic dose:** It is prescribed in pregnant females in rheumatic heart disease, cardiomyopathies, cerebral edema, along with blood transfusion in severe anemia to prevent volume overload, hypertension with renal insufficiency and CHF, hypertensive emergencies and pulmonary edema.

**Dosage:** Furosemide 20–80 mg divided in 6–12 hourly (PO/IM/IV).

**Adverse drug reaction:** Common Adverse drug reaction include hypokalemia, metabolic alkalosis, hypomagnesemia, hyperuricemia, dehydration, hypotension and dose related ototoxicity.

**Drug interaction:** Loss of potassium potentiate digitalis toxicity. NSAIDs reduces diuretic efficacy. Corticosteroids enhance hypokalemia. Amino glycosides enhance ototoxicity, nephrotoxicity.

It is a FDA category C drug.

**Spironolactone**

**Introduction:** This is a potassium sparing diuretics. They do not produce hypokalemia.

**Pharmacology:** This is an aldosterone receptor antagonist acts at the distal segment of distal tubule.

**Mechanism of action:** It causes more sodium and water to pass into the collecting duct and then be excreted in urine. By inhibiting aldosterone-sensitive sodium reabsorption by this transporter, less potassium and hydrogen ion are exchanged for sodium and therefore less potassium and hydrogen excreted in the urine. This diuretic has relatively weak effects on overall sodium balance, so it is often used in
conjunction with Frusemide/loop diuretics to prevent hypokalemia.\textsuperscript{21}

**Indications:** Same as Frusemide and used in combination.

**Dosage:** 25–400 mg/day in 1–2 divided dosage.

**Adverse drug reaction:** Hypokalemia, metabolic acidosis, gynecomastia, gastritis and peptic ulcer.\textsuperscript{21}

**Drug interaction:** ACE inhibitors potentiate hyperkalemia. NSAIDs reduces diuretic efficacy.

**Diltiazem**

**Introduction:** It blocks the L type calcium channels of the heart and causes direct depression of the SA node and AV conduction and blocks the entry of calcium into the cells.

**Pharmacology:** It is a calcium channel blocker.

**Mechanism of action:** It causes vascular smooth muscle relaxation and vasodilatation, decrease contractility of cardiac muscle, conduction velocity inside heart and heart rate. Diltiazem is able to reduce arterial pressure by having both cardiac depressant and vasodilator actions without producing the same degree of reflex cardiac stimulation caused by dihydropyridines.\textsuperscript{22}

**Pharmacokinetics:** Absorption is 90–100%, peak at 3 hours. The oral bioavailability is 40–60% due to high first pass metabolism in liver. It is bound to plasma protein (80%). It is metabolized in liver and the active metabolites excreted in urine. The half-life is 2–6 hours.

**Indications:** Pulmonary/systemic hypertension. Angina and arrhythmias (PSVT and supraventricular), AF rate control.

**Dosage:** Available in 30 mg, 60 mg, 90 mg sustained release tablets, 30–60 mg/6 hourly, Half-life 3–4.5 hour. Can be taken once/twice/thrice daily. IV dosage 0.25 mg/kg over 3–5 min (max 20 kg), maintenance 5–15 mg/hr. (SVT, AF rate control).\textsuperscript{6}

**Adverse drug reaction:** More common adverse drug reaction are body ache, dryness or soreness of the throat, congestion, cough, fever, hoarseness, runny nose, tender lymph node and voice changes. The less common effects are chest pain, diarrhea, difficult breathing, lightheaded, flushing, headache, joint pain and loss of appetite, nausea and vomiting.

**Drug interaction:** It should not be given with beta blockers, excessive cardiac depression may occur. It increases plasma digoxin level by decreasing its excretion, toxicity may develop.

**Monitoring:** By heart rate monitoring.

It is a FDA category C drug, compatible with breastfeeding.

**Lidocaine Hydrochloride**

**Introduction:** It is an antiarrhythmic drug used in ventricular arrhythmias.

**Pharmacology:** It is a membrane stabilizing antiarrhythmic agent.

**Mechanism of action:** It suppresses automaticity in His-Purkinje system and spontaneous depolarization of the ventricles during diastole and thereby controls arrhythmias.\textsuperscript{23}

**Pharmacokinetics:** It absorbs from GI tract and passes into hepatic circulation. Only 35% of oral dose reaches systemic circulation unchanged. Onset of action in IV route 45–90 sec and in IM route 10 mins. Duration of action up to 10–20 min in IV route. Plasma concentration of 1–5 µg/mL are required to suppress ventricular arrhythmias, concentration of >5 µg/mL associated with toxicity. It crosses blood brain barrier and placenta. It secretes into milk. It binds to plasma proteins in 60-80% cases. It is metabolized in liver and excreted in urine. It has half-life of 1.5–2 hours.\textsuperscript{24}

**Dosage:** IV/IM, preferred is IV, 1–3 mg/kg at 20–50 mg/min, maintenance 1–4 mg/min, used for VT.\textsuperscript{6} Preparations available in 40, 100, 200 mg/mL. For ventricular arrhythmias-IV bolus dose administered at a rate of 25–50 mg/minute (0.5–0.7 mg/kg/min) and up to 1–1.5 mg/kg (50–100 mg/kg) administered as rapid IV
injection. Can be repeated after 5–10 minutes if necessary, up to a total of 3 doses/up to 3 mg/kg. For cardiac arrest start at 1–1.5 mg/kg as rapid IV injection repeated at 5–10 minutes if necessary, up to a total of 3 doses/up to 3 mg/kg.\textsuperscript{23}

If arrhythmias recur during maintenance infusion 0.5 mg/kg bolus dose administered and infusion rate increased to a maximum of 4 mg/minute.

**Contraindications:** Severe degree heart block and known hypersensitivity.

Precaution-constant ECG monitoring required. To discontinue infusion if cardiac depression occur.

**Adverse drug reaction:** Hypersensitivity reactions. Nervous system—muscle twitching or tremors, seizure, unconsciousness and coma (in high doses). Cardiovascular system—possibility of hypotension, arrhythmias, heart block, cardiovascular collapse and bradycardia. Respiratory system—respiratory depression in high doses. Possibility of local thrombophlebitis in prolonged IV infusions.\textsuperscript{23}

It is FDA pregnancy category B drug. It is secreted in breast milk so to be used with caution.

**Pulmonary Vasodilators**

**Sildenafil**

**Pharmacology:** It is a selective inhibitor of phosphodiesterase type-5 (PDE5). PDE5 is known to enhance nitric oxide-mediated vasodilatation by inhibiting degradation of cyclic GMP in patients with/without heart failure.\textsuperscript{25}

**Mechanism of action:** It lowers the pulmonary arterial pressure and has been shown to improve arterial oxygenation in pulmonary hypertension. It significantly increases exercise capacity. It improves symptoms of right sided heart failure by reducing workload of the right ventricle of the heart.

**Pharmacokinetics:** Oral bioavailability of sildenafil is 40% and peak blood levels are attained in 1–2 hour. It is metabolized by the CYP3A4 and an active metabolite is produced. The half-life is 4 hours.

**Indications:** Pulmonary hypertension in rheumatic heart disease and Eisenmenger’s syndrome.

**Contraindication:** Severe hepatic/renal impairment, hypotension, recent stroke or heart attack. When taking nitric oxide donors like nitroglycerine and hereditary degenerative retinal disorder.

**Dosage:** 20 mg tds.

**Adverse drug reaction:** It can cause headache, flushing, nasal congestion, and impaired vision including photophobia or blurred vision and indigestion. Severe adverse drug reactions can occur rarely. Those are hypotension, myocardial infarction, ventricular arrhythmias, stroke, increased intraocular pressure and sudden hearing loss.\textsuperscript{26}

**Drug interaction:** Protease inhibitors used in HIV can increases adverse drug reaction by inhibiting the metabolism of sildenafil. Those who are on protease inhibitor can reduce the sildenafil dose to 25 mg/48 hours. Erythromycin and cimetidine can lead to prolonged plasma half-life. If taken with alpha blocker may cause low blood pressure. Both should be taken at 4 hour interval.

It is a FDA category B, drug compatible with breastfeeding.

**Anticoagulation in Pregnancy**

There are many cardiovascular disease conditions require the initiation or maintenance of anticoagulation during pregnancy those include, patients using mechanical heart valves, acute deep vein thrombosis or thromboembolism or history of venous thromboembolism during pregnancy, atrial fibrillation. The three most common agents considered for use during pregnancy are warfarin, unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH).
**Warfarin**

**Introduction:** In 1954, it was approved for use as a medication. Most widely prescribed anticoagulant. The name Warfarin was taken from its discovery the organization that funded the key research “WARF” (Wisconsin Alumni Research Foundation) and the ending-arin is due to link with coumarin.

**Pharmacology:** It is a synthetic derivative of dicoumarol, a 4-hydroxycoumarin derived mycotoxin anticoagulant.

**Mechanism of action:** Warfarin, produces anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2, 3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the carboxylation of glutamate residues to γ-carboxyl glutamate (Gla) on the N-terminal region of vitamin K-dependent proteins-coagulation factors II, VII, IX and X, that binds to Ca²⁺ and coagulation sequence to proceed. By inhibiting the vitamin K conversion cycle, warfarin induces hepatic production of partially decarboxylated proteins with reduced coagulant activity. Carboxylation promotes binding of the vitamin K dependent coagulation factors to phospholipid surfaces, thereby accelerating blood coagulation. The reduced form of vitamin K (vitamin KH₂) is required for γ-carboxylation. Coumarins inhibits the enzyme vitamin K epoxide reductase and block the formation of vitamin KH₂, thereby limiting the γ-carboxylation of the vitamin K dependent coagulant proteins. The anticoagulant effect of coumarins can be overcome by low doses of vitamin K which bypasses vitamin K epoxide reductase. Warfarin interferes with the carboxylation of Gla proteins synthesized in bone, which contribute to fetal bone abnormalities when used in pregnancy but it does not affect bone metabolism in children or adults.

**Pharmacokinetics:** Warfarin is rapidly absorbed from the gastrointestinal tract. It has high bioavailability and reaches maximal blood concentrations 90 minutes after oral administration. It has half-life of 36-48 hours, bound to plasma albumin and accumulates in the liver. The genetic and environmental factors, including common mutations in the gene coding for cytochrome P450, the hepatic enzyme responsible for oxidative metabolism of the warfarin S-isomer influences the relationship between the dose and the response of warfarin. Many genetic polymorphisms in cytochrome P450 have been described that are associated with requirements of lower dose and higher complication rates (bleeding). It crosses placenta, can cause warfarin embryopathy in first trimester exposure patients and is secreted in the milk, however not enough to affect the infant.

**Dosage and monitoring:** 4–5 mg, increase up to 10 mg/day. After beginning oral warfarin the anticoagulant effect observed within 2–7 days. Heparin should be given concurrently with warfarin for ≥4 days if a rapid effect is required. Average maintenance dose is 5 mg/day which usually results in an INR (patient prothrombin time/mean normal prothrombin time) of ≥2.0 after 4 or 5 days. Heparin can be stopped once the INR comes to therapeutic range for 2 days. For nonemergency situation (e.g. chronic atrial fibrillation) treatment can be started outpatient wise and satisfactory anticoagulation within 6 days can be achieved with a dose of 4–5 mg/day. In patients sensitive to warfarin, the elderly and in those at increased risk of bleeding should be treated with lower doses (<4–5 mg).

**Monitoring of treatment with warfarin:** Daily prothrombin time (PT) and INR to be done till the therapeutic range (INR 2–3) has been achieved and sustained for 2 consecutive days. After that PT and INR can be done 2–3 times weekly for 1–2 weeks and then less often as required to the stability of the results. Once the INR becomes stable, the frequency of testing can be as long as 4 weeks intervals. Frequent monitoring is resumed when dose adjustments are required—when there is change in diet of the patient, concurrent medication changes, poor compliance or alcohol intake by the patient.

**INR therapeutic range:** The therapeutic range for INR is between 2 and 4. INR <2 may
increase the risk of thromboembolism. The risk of bleeding increases when INR of the patient exceeds 4 and the risk rises sharply with INR values of >5. When INR is elevated, to lower it the first step is to stop warfarin; the second step is to administer vitamin K and the third and most rapidly effective step is to infuse fresh frozen plasma or prothrombin concentrate. After warfarin stopped INR comes back to 2–3 after 4–5 days but it can decline within 24 hr with vitamin K.

**Precaution during pregnancy:** During the first trimester of pregnancy, warfarin therapy should be avoided. And in some special circumstances it is avoided throughout pregnancy. In women with mechanical prosthetic heart valves warfarin is recommended in second and third trimesters of pregnancy and to be converted to heparin/LMWH at 38 weeks and elective induction to be planned at 40 weeks of pregnancy. Lesser dose of heparin required to prevent maternal thromboembolism also might outweigh the risk of warfarin embryopathy during first trimester. If administer to nursing mother it does not affect feeding infant.

**Adverse drug reactions**
- **Bleeding due to high INR values:** In a clinical situation when INR is above therapeutic range but <5, with no significant bleeding and if patient does not require rapid reversal for surgical intervention, then the dose of warfarin can be reduced or the next dose can be omitted and to be resumed (at a lower dose) when INR becomes normal. If INR is between 5–9 and the patient is not bleeding and has no risk factor that predispose to bleeding, the next ½ doses of warfarin omitted and reinitiated after INR falls at a lower dose. Vitamin K 1–2.5 mg orally given if the patient is high-risk for bleeding. If rapid reversal is required in case of urgent surgery or dental extraction oral vitamin K 2–5 mg and may repeat dose vitamin K 1/2 mg if INR remains high after 24 hours. If INR is >9 and clinically there is no significant bleeding, oral vitamin K 3–5 mg can be given and may repeat if necessary. If INR is >20 and rapid reversal is required because of serious bleeding, vitamin K should be given as slow intravenous infusion in a dose of 10 mg, supplemented with transfusion of fresh plasma or prothrombin complex concentrate. Additional dose of vitamin K may be necessary every 12 hours. After administration of high dose of vitamin K, if warfarin is to be resumed, additional heparin should be given until there is reversal of vitamin K effects and response to warfarin of the patient is seen.

- **Other adverse drug reactions include alopecia, cutaneous necrosis, dermatitis and diarrhea.** Extensive thrombosis of venules and capillaries within subcutaneous fat can lead to skin necrosis (rare) which is observed on third to eighth day of therapy. This may be associated with warfarin induced protein C or S deficiency but exact pathogenesis not known. With this complication warfarin is contraindicated and heparin to be given. As heparin at long-term can cause osteoporosis restart of warfarin can be done with lower dose of 2 mg with heparin and gradually increase in several weeks.

- **Teratogenicity with warfarin:** Two types of birth defect can occur if exposed during developmental period. If exposed between 6th and 9th week the fetus is at risk of warfarin embryopathy. This is characterized by nasal and midface hypoplasia, and stippled vertebral and femoral epiphyses and vitamin K dependent clotting factors are not demonstrable in the embryo. Warfarin derivatives exert their teratogenic effect by inhibiting post-translational carboxylation of coagulation proteins. The risk of embryopathy is dose dependent >5 mg daily throughout first trimester. During second and third trimesters, the defects associated with fetal exposure to warfarin may cause hemorrhage leading to disharmonic growth and deformation from scarring in any organs. Defect may lead to agenesis of corpus callosum, Dandy Walker malformation, and midline cerebellar atrophy, microphthalmia, optic atrophy and blindness, developmental
delay and mental retardation. It may cause miscarriage, stillbirths also.\textsuperscript{33}

**Drug interactions:** Some commonly used drugs enhance the anticoagulant effect of warfarin. Broad spectrum antibiotics (Ceftriaxone and Cefoperazone) and sulfonamides inhibit gut flora and reduce vitamin K production, aspirin, indomethacin, phenytoin, amiodarone and metronidazole inhibit warfarin metabolism. Phenylbutazone, sulfinpyrazone, metronidazole and trimethoprim-sulfamethoxazole potentiate its effect by inhibiting clearance of S-warfarin. Amiodarone inhibit the metabolic clearance and potentiate the action of warfarin. Anticoagulant effect of warfarin is inhibited by barbiturates, rifampicin and carbamazepine by increasing hepatic clearance. In patients consuming green vegetables or vitamin K containing supplements like weight reducing diet and in patients receiving intravenous vitamin K supplements can reduce the anticoagulant response to warfarin.

It is a FDA category X drug.

**Unfractionated Heparin**

**Introduction:** McLean in 1916 discovered Heparin.\textsuperscript{34} Brinkhous and associates demonstrated that heparin requires a plasma cofactor for its anticoagulant activity more than 20 years later, and that was named antithrombin III by Abildgaard in 1968 but now referred as antithrombin (AT).\textsuperscript{35} Rosenberg Lindahl, and others in 1970s, elucidated the mechanism for Heparin/AT interaction. The active center serine of thrombin and other coagulation enzymes is inhibited by an arginine reactive center on the AT molecule and that heparin binds to lysine sites on AT, producing a conformational change at the arginine reactive center that converts AT from a slow, progressive thrombin inhibitor to a very rapid inhibitor. AT binds covalently to the active serine center of coagulation enzyme, and then heparin dissociates from the ternary complex and can be reutilized. Later on it was discovered that heparin binds to and potentiate the activity of AT through a glucosamine unit contained within a pentasaccharide unit.\textsuperscript{36}

**Pharmacology:** The molecular size (3000-30000 Da), anticoagulant activity (only 1/3rd have this function) and pharmacokinetic properties (depends on chain length) of heparin is heterogeneous. High molecular weight species of heparin cleared from circulation early than low molecular weight species. This is responsible for the difference in the relationship between plasma heparin concentration (measured in antifactor Xa units) and the activated thromboplastin times (aPTT).

**Mechanism of action:** After administration of heparin one third of its dose binds to AT which is responsible for the anticoagulant action and the remaining two third has minimal therapeutic action. The heparin AT complex inactivates a number of coagulation enzymes, including thrombin factor IIa and factors Xa, IXa, XIIa, and Xla.\textsuperscript{36} Thrombin and factor Xa are the most responsive to inhibition. By inactivating thrombin, heparin prevents fibrin formation as well as inhibits thrombin-induced activation factor V and factor VIII.

Heparin prolongs bleeding time in human. Interaction of heparin with platelets and endothelial cells may contribute to heparin induced bleeding by a mechanism independent of its anticoagulant effect. Heparin increases vessel wall permeability, suppresses the proliferation of vascular smooth muscle cells and suppresses osteoblast formation and activates osteoclasts, effects that promote bone loss.\textsuperscript{37}

At low concentrations of heparin, factor Xa mediated conversion of prothrombin to thrombin is selectively affected. In higher doses, it prevents platelet aggregation.\textsuperscript{38}

**Pharmacokinetics:** Heparin is a large molecule so not absorbed orally. It is given continuous IV infusion and subcutaneous (SC) injection. On SC injection, the anticoagulant effect may delay for 1–2 hours. In blood-stream it binds to number of plasma proteins, endothelial cells and macrophages. After binding to endothelial cell receptors and macrophages heparin is depolymerized and cleared from circulation. Heparin does not cross blood brain barrier or placenta. It is metabolized in liver by heparinase
enzyme and excreted through urine. The half-life of heparin is dose-dependent and can be prolonged to 1–4 hours at doses of more than 100 U/Kg.

**Dosage:** Therapeutic dose of heparin is 10000–35000 U/SC/24 hour. Prophylactic dose of heparin is 5000–10000 U Sc/8–12 hour. For women with mechanical prosthetic valves, heparin should be started with daily dose of 35000 U. Monitoring with patients on heparin should be performed with either activated partial thromboplastin time or heparin assays at least twice weekly. Higher heparin doses may be required in third trimester because of an increase in heparin-binding proteins.

**Adverse drug reaction:** Bleeding can occur if over dosage and manifest as hematuria. The antidote is protamine sulfate can be given on a weight by weight basis for the treatment of heparin induced bleeding. With proper monitoring, this can be prevented. Heparin may induce thrombocytopenia which may lead to thromboembolic events. Caution with aspirin and other antiplatelet agent. Contraindication of use are bleeding disorder, history of heparin induced thrombocytopenia, severe hypertension, ocular and neurosurgery, subacute bacterial endocarditis (risk of embolism), tuberculosis (risk of hemoptysis, cirrhosis and renal failure.

**Monitoring:** Activated partial thromboplastin time is used to monitor the therapeutic levels. It is kept 1.5–2.5 times the patient’s pretreatment levels.

It is compatible with breastfeeding (ACOG 2011).

**Low Molecular Weight Heparins**

**Introduction:** The LMWHs are developed for clinical use because of LMWH has reduced antifactor IIa activity relative to antifactor Xa activity and superior pharmacokinetic properties in comparison to UFH.

**Pharmacology:** LMWH are formed from Heparin by reducing the molecular size while still inhibiting the factor Xa. LMWH has mean molecular weight of 4500–5000 Da.

**Mechanism of action:** LMWH produce their anticoagulant effect by activating AT due to their pentasaccharide sequence found in <1/3rd of molecules. They selectively inhibit factor Xa with little effect on factor IIa by bringing only a conformational change in antithrombin III. As a result they have less effect on aPTT, lesser antiplatelet action and thus less interference with hemostasis.

**Pharmacokinetics:** LMWH has a longer plasma half-life (because of less binding to macrophages and endothelial cells) and better bioavailability at low doses than heparin and have more predictable dose response (because of reduced binding to plasma protein). They have subcutaneous bioavailability of 70–90% with minimum variability in response. They have a longer half-life of 4–6 hour so once daily dose is feasible. LMWH cleared through kidney and biological half-life prolonged in renal failure patients.

**Dosage:** One mg/kg body weight, twice daily. For patients with mechanical prosthetic valve LMWH should be given subcutaneously at a dose of 100 anti-Xa U/kg twice daily. The dose is adjusted to maintain the anti-Xa level between 0.5 and 1.0 U/mL, 4–6 hour after injection.

**Adverse drug reaction:** LMWH has reduced binding capacity to platelet so less chance of heparin induced thrombocytopenia and it has less binding to osteoblasts leading to less bone loss. It is compatible with breastfeeding.

**Monitoring:** aPTT is not prolonged so lab monitoring is not needed.

**Preparations:** Enoxaparin available in 20 mg and 40 mg prefilled syringe.

**Use in mechanical valves:** For anticoagulation for mechanical valves, LMWH is definitely inadequate and has high associated maternal mortality rate. Even full anticoagulation with unfractionated heparin or LMWH is associated with valvular thrombosis.
Options of anticoagulation use in pregnancy in women with prosthetic valves: Regimes recommended by the American College of Chest Physicians for anticoagulation in pregnancy with prosthetic valves—any one of the following (William 24th edition).

- Adjusted LMWH throughout pregnancy twice daily. The doses should be adjusted to achieve the peak anti-Xa level 4 hours after subcutaneous injection
- Adjusted UFH throughout pregnancy every 12 hours. Dose adjusted to maintain aPTT at least twice control or attain an antiXa level of 0.35–0.70 U/mL.
- LMWH or UFH till 13 weeks, then warfarin substitution, and at 38 weeks of pregnancy LMWH or UFH resumed and planned labor induction at 40 weeks or until close to delivery.
- In very high-risk women, warfarin throughout the pregnancy and substitution with LMWH or UFH close to delivery, at 38 weeks of pregnancy and planned labor induction at 40 weeks. In addition, low dose aspirin 75–100 mg daily should be given.
- Heparin/LMWH should be discontinued 12 hours before planned induction of labor. Heparin/LMWH should be started postpartum and overlapped with warfarin for 4–5 days.

It is a FDA category B drug.

Antibiotic Prophylaxis

Patients with heart disease who are at highest risk of developing infective endocarditic (IE) include—a prosthetic heart valve, valve repair with prosthetic material, a prior history of IE, and many congenital cyanotic heart diseases like single ventricle state, transposition of the great arteries and tetrlogy of Fallot even if the abnormalities repaired, valvulopathy after heart transplantation. These patients must require IE prophylaxis prior to certain procedures during pregnancy like undergoing dental procedure that involve manipulation of the tissue of the gums, the peripheral region of the teeth or perforation of the lining membranes of the gums such as tooth extractions, dental scaling or drainage of a dental abscess. Any oral or upper respiratory tract procedure also requires IE prophylaxis.

Antibiotics Recommendations by American Heart Association

Single dose of antibiotics to all highest risk patient is necessary. All heart disease patients who are of moderate and low risk for infective endocarditis do not require any antibiotic prophylaxis. Usually penicillin is given. People who are allergic to penicillin can be treated one hour before the procedure with an alternate antibiotic. Patients those are unable to take oral medication can be treated with an antibiotic injection 30 min before the procedure. Antibiotic prophylaxis is not recommended by AHA for any genitourinary or gastrointestinal procedures.

A pregnant patient who has at high-risk for IE does not usually need antibiotic prophylaxis before a normal vaginal delivery or cesarean section in the absence of pelvic infection. Antibiotics may be recommended before labor or cesarean section for complications related to Group B Streptococcus like PROM and PPROM, etc.

ACOG 2011 recommendation of antibiotic prophylaxis for infective endocarditis in high-risk women.

Standard (IV): Ampicillin 2 g or cefazolin or ceftriaxone 1 g penicillin allergic (IV): cefazolin or ceftriaxone 1 g or clindamycin 600 mg. Oral amoxycillin 2 g, Azithromycin 500 mg PO, Cephalexin 500 mg PO. These drugs are administered as close to 30–60 minutes before anticipated delivery time as is feasible.

REFERENCES


