, visit our website www.jaypeebrothers.com, for detailed information on obstetrics & gynecology books, visit our website www.jaypeebrothers.com

FOGSI

Medical Disorders in Pregnancy

Series Editor
Hrishikesh D Pai

Editors
Manoj Chellani
Hrishikesh D Pai
Yashodhara Pradeep
Parikshit Tank
Niranjan Chavan

Co-Editors
Jyoti Jaiswal
Neema Acharya



Foreword
Hrishikesh D Pai

JAYPEE

Contents

1. **Anemia in Pregnancy** 1
   Archana Singh
2. **Hypertensive Disorders of Pregnancy** 8
   Jyoti Ramesh Chandran
3. **Diabetes in Pregnancy** 16
   Pawan Preet Mann Gill
4. **Obesity in Pregnancy** 28
   Revati Nitin Rane
5. **Thyroid Disorders in Pregnancy** 37
   Neema Acharya, Sourya Acharya, Samarth Shukla
6. **Asthma in Pregnancy** 42
   Jyoti Jaiswal, Supriya Gupta
7. **Heart Diseases in Pregnancy** 50
   Divya Agrawal
8. **Liver Diseases in Pregnancy** 64
   Shweta Kumari
9. **Renal Disorders in Pregnancy** 72
   Manoj Chellani
10. **Epilepsy in Pregnancy** 83
    Rajasri G Yaliwal, Neelamma Patil, Sangamesh B Bhagavati
11. **Rh Alloimmunization** 89
    Mariyam Faruqi, Devyani Misra
12. **Systemic Lupus Erythematosus in Pregnancy** 99
    Sonal Gupta
13. **Hepatitis B Infection in Pregnancy** 108
    Padma Shukla, Sonal Agrawal
14. **Urinary Tract Infection in Pregnancy** 113
    Mamta
15. **Dengue in Pregnancy** 118
    Richa Sharma, Ajay Adhikari

16. HIV in Pregnancy 125
Indira Palo

17. SARS-CoV-2 during Pregnancy 133
Sudesh Agrawal

18. Pregnancy-related Constipation 143
Saket Kumar, Lakshit Tomar, Vijay Prakash Singh

Index 149

Chapter 15

Dengue in Pregnancy

Richa Sharma, Ajay Adhikari

INTRODUCTION

Dengue fever is an arthropod borne viral illness which causes significant mortality and morbidity across the world including in pregnant females. It is commonly referred to as breakbone fever or seven day fever. The culprit organism is a single stranded ribonucleic acid (RNA) virus that belongs to *Flavivirus* family and has four different serotypes (DENV 1-4). Infection with any one of these serotypes provides lifelong immunity to that individual from that particular serotype.[1] *Aedes* mosquito that transmits the virus is commonly found in tropical countries such as India, which is why dengue is one of the leading causes of pyrexia in pregnant females in India. Despite rapid urbanization, an upward trend has been seen in the incidence dengue over past few decades.[2] This chapter will give insights on how this deadly disease further complicates pregnancy and how to effectively manage dengue in pregnancy.

EPIDEMIOLOGY

Majority of people affected by dengue are asymptomatic or have mild symptoms due to which its prevalence is highly underreported.[3] One study estimates around 390 million dengue infections across world every year out of which 96 million present with varying severity of symptoms.[4] Although there are no accurate figures depicting the burden of disease in pregnant females, it is known to cause adverse maternal and fetal outcomes. The reporting of dengue to the World Health Organization (WHO) has increased by more than eight times in couple of decades due to better communication between healthcare facilities and health ministries.

PATHOPHYSIOLOGY

Once the virus is injected into intradermal tissue following the bite of mosquito, skin macrophages and dendritic cells are known to be its primary targets. These cells are then believed to reach lymph nodes from where they spread to other organs via lymphatic system. Symptom onset occurs after a phase of viremia which lasts up to 48 hours. Patient's immune response to virus play a key role in determining whether the infection will be asymptomatic or progress to severe dengue with increased microvascular permeability and shock. **Figure 1** summarizes pathophysiology of dengue virus.

MATERNAL TRANSMISSION

Although mosquito vectors are most common mode of transmission of dengue virus, there is some evidence of transmission by pregnant mother to her baby as well. However, rate of vertical transmission is found to be low and often linked with the timing of dengue

JAYPEE BROTHERS

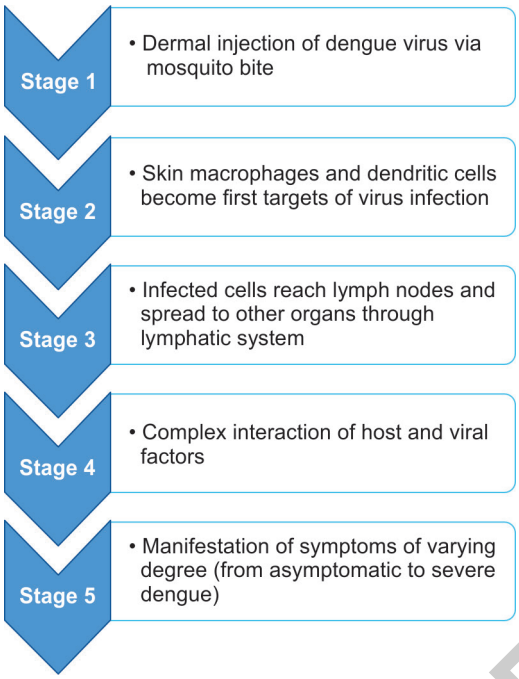


Fig. 1: Pathophysiology of dengue virus.

infection during the course of pregnancy.[5] Incidence of maternal transmission is significant if infection occurs within 5 weeks of delivery. A positive correlation between pregnant female with dengue fever and complications such as preterm birth, low-birth-weight, and fetal distress has also been established.[6]

CLINICAL FEATURES

Spectrum of the disease may vary from being asymptomatic to undifferentiated fever to hemorrhagic complications to shock. Incubation period generally lasts from 2 to 7 days followed by prodromal phase of headache and malaise.

Dengue fever is generally divided into three phases as depicted in **Box 1**.

In severe dengue, organs such as liver, kidney, heart, central nervous system (CNS) and other isolated organs may be involved further complicating the disease and increasing mortality. Dengue hemorrhagic fever, disseminated intravascular coagulation, dengue shock syndrome, acute respiratory distress syndrome (ARDS), encephalitis and myocarditis are few of the life-threatening complications.

Thorough assessment of pregnant females is vital because their symptoms of dengue may be similar to preeclampsia.

BOX 1: Clinical phases of dengue fever.

Febrile phase
- It is characterized by high grade fever which is sudden in onset and reaches approximately 40°C
- Fever typically lasts for 2–7 days and is continuous or saddleback in type[7]
- Associated symptoms generally include erythema, myalgia, arthralgia, headache, nausea, and vomiting

Critical phase
- It lasts up to 2 days and is characterized by defervescence. There is increased capillary permeability in this phase
- Decreased platelet count and increased hematocrit are common laboratory findings
- Special attention to warning signs must be given in this phase. Warning signs which indicate toward severe disease and increased risk of mortality include abdominal pain or tenderness, persistent vomiting, ascites, pleural effusion, mucosal bleed, and hepatomegaly

Recovery phase
- The fluid leaked in extravascular compartments due to capillary leak is slowly reabsorbed
- Bradycardia may be observed

WORLD HEALTH ORGANIZATION CASE DEFINITION OF DENGUE

The disease is classified in following case definitions for the purpose of better identification and prompt initiation of treatment.[8] **Box 2** depicts the WHO case definition of dengue.

JAYPEE BROTHERS

BOX 2: WHO case definition of dengue.

Probable dengue fever
- Exposure in endemic area
- Fever
- Any two of following—nausea/vomiting, rash, aches/pains, positive tourniquet test, leukopenia, or any warning sign

Dengue with warning signs
- Probable dengue with one of the following—abdominal pain or tenderness, persistent vomiting, signs of fluid accumulation, mucosal bleed, hepatomegaly >2 cm, rapid rise in hematocrit, and fall in platelet count

Severe dengue
- Severe plasma leakage leading to shock (dengue shock syndrome) or respiratory distress
- Severe hemorrhagic complications
- Sever organ involvement (liver, CNS, kidney, cardiomyopathy, pancreatitis, acute lung injury, and DIC)

(CNS: central nervous system; DIC: disseminated intravascular coagulation; WHO: World Health Organization)

CHALLENGES IN DIAGNOSIS OF DENGUE DURING PREGNANCY

Hemodilution is normal physiological process during pregnancy but it hampers with diagnosis of dengue and its complications. Hemodilution masks thrombocytopenia, leukopenia, and increased hematocrit levels which are early laboratory markers of severe dengue.[9] A few common obstetric conditions are known to cause elevation of liver enzymes which further creates confusion as it is also a marker of hepatic involvement in dengue. Pregnancy being a hypercoagulable state may also lead to misdiagnosis of some other complications of dengue like disseminated intravascular coagulation or dengue hemorrhagic fever.[10] Vomiting which is a warning sign of severe dengue may also be easily misconstrued as hyperemesis during pregnancy.

LABORATORY DIAGNOSIS

Various virus isolation methods and serological methods play key role in diagnosis of the disease. Different techniques may be used at different time of presentation. During first week of infection, virus can be isolated by reverse transcriptase-polymerase chain reaction (RT-PCR). Another method is detection of NS1 antigen on rapid diagnostic test kits, which is cheaper and requires less skill. Serological methods like enzyme-linked immunosorbent assay (ELISA) detect antidengue antibodies. Immunoglobulin M (IgM) antibodies are detected from 1 week to 3 months of infection while IgM antibodies are detected from months to years.

Patient presenting during first week of illness should be tested for both virus isolation by RT-PCR or NS1 detection and serological evaluation.

Once diagnosed it should be kept in mind that dengue is a notifiable disease and must be reported to local health bodies.

DIFFERENTIAL DIAGNOSIS

Other causes of pyrexia in pregnancy must always be excluded before making the final diagnosis. Malaria, chikungunya, influenza, and measles are few other common causes of pyrexia in pregnancy. Detailed history, immunization, travel history, and history of exposure to mosquitoes are important to reach the diagnosis. Sometimes serological tests may show false positive results due to infection from other *Flavivirus* such as yellow fever and *Zika* virus.

ADVERSE MATERNAL OUTCOMES IN DENGUE WITH PREGNANCY

Various studies have established increased risk of adverse maternal and fetal outcomes

JAYPEE BROTHERS

in pregnant females with dengue infection. Organ dysfunction or multiorgan failure is found to be associated with poor prognosis in pregnant as well as nonpregnant females with dengue,[11] hence special attention and intensive care unit (ICU) care must be given to pregnant female suffering from dengue with any clinical or laboratory evidence suggesting organ failure such as acute kidney injury, hepatic failure, and ARDS. Elevated liver enzymes or serum creatinine are independent risk factors of poor prognosis in dengue with or without pregnancy.[12]

Previous studies have indicated that there is no significant increase in rate of cesarean section in pregnant females with dengue.[13] Although marked increased risk of postpartum hemorrhage (PPH) due to dengue-related thrombocytopenia has been observed. Rate of PPH in dengue with pregnancy is fairly high (anywhere between 2 and 30% of all deliveries).[14] Hence, intense monitoring of pregnant female with dengue in third stage of labor along with timely and judicious transfusion of blood components is important.

A positive correlation has also been found between dengue and pregnancy and risk of miscarriage in a prospective case control study conducted in 2012.[15] The rate of stillbirth in pregnant female with dengue is estimated to be between 3.8 and 13.1% as per various studies;[16] however, exact mechanism of this increased rate of stillbirth is not yet understood. Whether this increase in incidence of stillbirth is due to hyperthermia or dengue virus itself is yet to be analyzed in future studies.

ADVERSE FETAL OUTCOMES IN DENGUE WITH PREGNANCY

Just like mother dengue in pregnancy can be equally hazardous for the health of fetus. Various complications to fetus should come in mind of obstetrician managing pregnant female suffering from dengue. Dengue-related hyperthermia has been linked to increased risk of congenital malformations in fetus, such as neural tube defects.[17] Preterm birth and low-birth-weight are some other adverse outcomes for fetus that have shown positive correlation with dengue in pregnancy.[18] A meta-analysis in 2016 again reiterated increased risk of low-birth-weight and preterm births in dengue with pregnancy.[19] The reason for these adverse events is believed to be due to maternal illness rather than direct effect of the virus on the fetus. Mothers with severe dengue and complications like hemorrhagic fever showed greater risk of adverse fetal outcomes. There is also a very high chance of preterm birth within 10 days of onset of symptoms in mothers suffering from dengue.

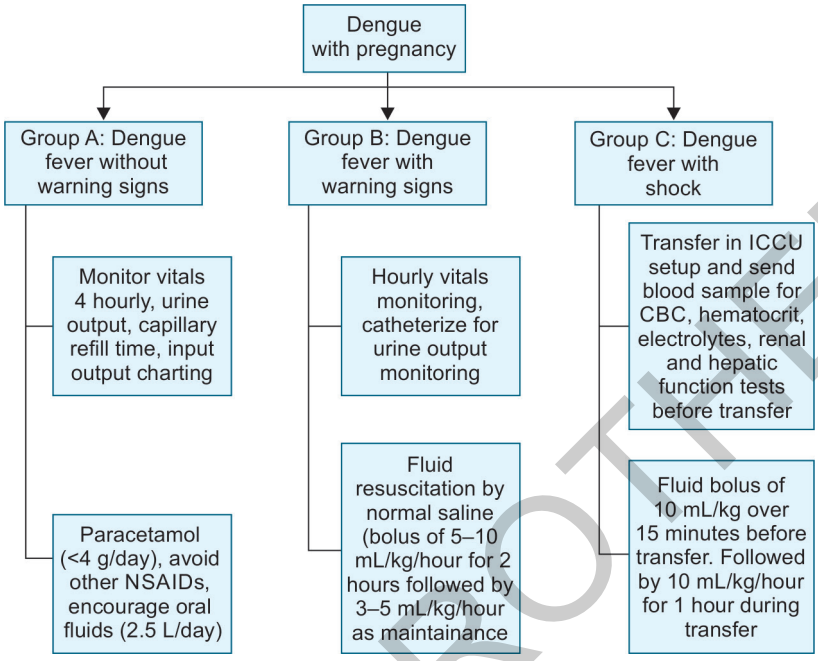
Not all studies have shown such devastating consequences for the baby but still there is enough evidence in literature for the treating obstetricians to be alarmed by the situation. Considering all the maternal and fetal risks we have discussed earlier, it becomes imperative to manage all symptoms and complications of dengue in pregnancy timely and promptly.

MANAGEMENT OF DENGUE IN PREGNANCY

Before beginning the management part it is important to note that dengue at any stage of pregnancy is in no way an indication for termination of pregnancy. The most important part of management of dengue fever is identification of onset of critical phase. Clinically evident effusion or ascites indicates that the critical phase has already begun several hours ago. The onset of critical phase

JAYPEE BROTHERS

Flowchart 1: Management protocols of dengue in pregnancy.



(CBC: complete blood count; ICCU: intensive coronary care unit; NSAIDs: nonsteroidal anti-inflammatory drugs)

can be accurately depicted by beginning of rise in hematocrit levels.[20] Declining platelet counts also indicate that patient has risk of landing in critical phase in next 24 hours.

It is imperative that all pregnant females with suspected or confirmed dengue fever be admitted in hospital for close monitoring purpose. For the purpose of proper management patients are divided into three groups. Management protocols are summarized in **Flowchart 1**.

Dengue fever without warning signs should be managed by encouraging oral fluids and paracetamol. Use of other nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen or diclofenac must be avoided. In case of dengue fever with warning signs or dengue fever with shock, normal saline is the fluid of choice for resuscitation and is preferred over ringer lactate or dextrose sodium chloride solution (DNS). Use of colloids in dengue fever with shock is justified if there is no clinical improvement after two bolus of crystalloids.

Prophylactic platelet transfusion is not indicated; however, if delivery is inevitable within 6 hours, transfusion can be done to maintain platelet count over 50,000 per μL for normal delivery and over 75,000 per μL for cesarean section. Similarly, blood loss should be recognized and whole blood or packed cell transfusion should be initiated before blood loss exceeds 500 mL. Oxytocin infusion to prevent PPH is common practice in dengue with pregnancy to avoid excessive blood loss. Operative delivery should be performed purely for obstetric indications and planned induction surgery must be avoided. There is no role of use of steroids, immunoglobulins, or prophylactic antibiotics.

It is suitable to discharge the patient only when she is afebrile for >1 day, hematocrit levels are normal and platelet counts are in rising trend.

JAYPEE BROTHERS

CONCLUSION

Dengue is one of the leading causes of pyrexia in pregnancy and has the potential to complicate the pregnancy and adversely affect maternal and fetal health. Past two decades have seen alarming increase in the incidence of dengue with or without pregnancy. The severity of disease depends very much upon the patient's immune response to virus. Majority of patients are asymptomatic or have mild symptoms at presentation. Special attention must be given to warning signs as they indicate severe disease with fatal complications. Symptoms and signs of dengue may often be confused with preeclampsia and some other physiological events during pregnancy, hence detailed history and timely laboratory investigation helps clinch the diagnosis. Due to heightened risk of adverse maternal and fetal complications such as PPH, low-birth-weight, and preterm delivery management protocols should be followed precisely in dengue with pregnancy. Use of fluids and blood components should be prompt and judicious. All pregnant patients with dengue must be managed in inpatient department (IPD) and be discharged only when they are afebrile for 24 hours, platelet counts are on rising trend, and risk of complications have subsided after critical phase.

REFERENCES

1. Seixas G, Salgueiro P, Bronzato-Badial A, Gonçalves Y, Reyes-Lugo M, Gordicho V, et al. Origin and expansion of the mosquito Aedes aegypti in Madeira Island (Portugal). Sci Rep. 2019;9(1):2241.
2. Sharma M, Glasner DR, Watkins H, Puerta-Guardo H, Kassa Y, Egan MA, et al. Magnitude and functionality of the NS1-specific antibody response elicited by a Live-attenuated tetravalent dengue vaccine candidate. J Infect Dis. 2020;221(6): 867-77.
3. Waggoner JJ, Gresh L, Vargas MJ, Ballesteros G, Tellez Y, Soda KJ, et al. Viremia and clinical presentation in nicaraguan patients infected with zika virus, chikungunya virus, and dengue virus. Clin Infect Dis. 2016; 63(12):1584-90.
4. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-7.
5. Basurko C, Matheus S, Hildéral H, Everhard S, Restrepo M, Cuadro-Alvarez E, et al. Estimating the risk of vertical transmission of dengue: a prospective study. Am J Trop Med Hyg. 2018;98(6):1826-32.
6. Pouliot SH, Xiong X, Harville E, Paz-Soldan V, Tomashek KM, Breart G, et al. Maternal dengue and pregnancy outcomes a systematic review. Obstet Gynecol Surv. 2010; 65(2):107-18.
7. Ng DH, Wong JG, Thein TL, Leo YS, Lye DC. The Significance of Prolonged and Saddleback Fever in Hospitalised Adult Dengue. PLoS One. 2016;11(12):e0167025.
8. Wharton-Smith A, Green J, Loh EC, Gorrie A, Omar SFS, Bacchus L, et al. Using clinical practice guidelines to manage dengue: a qualitative study in a Malaysian hospital. BMC Infect Dis. 2019;19(1):45.
9. Malhotra N, Chanana C, Kumar S. Dengue infection in pregnancy. Int J Gynecol Obstet. 2006;94:131-2.
10. Basurko C, Carles G, Youssef M, Guindi WEL. Maternal and foetal consequences of dengue fever during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2009;147:29-32.
11. Padyana M, Karanth S, Vaidya S, Gopaldas JA. Clinical profile and outcome of dengue fever in multidisciplinary intensive care unit of a Tertiary level Hospital in India. Indian J Crit Care Med. 2019;23:270-3.
12. Saroch A, Arya V, Sinha N, Taneja RS, Sahai P, Mahajan RK. Clinical and laboratory factors associated with mortality in dengue. Trop Doct. 2017;47:141-5.

JAYPEE BROTHERS

13. Tan PC, Rajasingam G, Devi S, Omar SZ. Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. Obstet Gynecol. 2008;111: 1111-7.
14. Tien Dat T, Kotani T, Yamamoto E, Shibata K, Moriyama Y, Tsuda H, et al. Dengue fever during pregnancy. Nagoya J Med Sci. 2018; 80:241-7.
15. Tan PC, Soe MZ, Lay KS, Sm W, Sekaran SD, Omar SZ. Dengue infection and miscarriage: a prospective case control study. PLoS Negl Trop Dis. 2012;6:e1637.
16. Carles G, Talarmin A, Peneau C, Bertsch M. Dengue fever and pregnancy. A study of 38 cases in French Guiana. J Gynecol Obstet Biol Reprod. 2000;29:758-62.
17. Edwards MJ. Review: hyperthermia and fever during pregnancy. Birth Defects Res A Clin Mol Teratol. 2006;76:507-6.
18. Xiong YQ, Mo Y, Shi TL, Zhu L, Chen Q. Dengue virus infection during pregnancy increased the risk of adverse fetal outcomes? An updated meta-analysis. J Clin Virol. 2017;94:42-9.
19. Paixão ES, Teixeira MG, Costa M, Rodrigues LC. Dengue during pregnancy and adverse fetal outcomes: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:857-65.
20. Ministry of Health. National Guidelines on Management of Dengue Fever and Hemorrhagic Fever in adults and children. Colombo, Sri Lanka: Ministry of Health; 2011.

JAYPEE BROTHERS

for detailed information on obstetrics & gynecology books, visit our website www.jaypeebrothers.com, for detailed information on obstetrics & gynec

Medical Disorders in Pregnancy

This book is a team work of highly experienced clinicians and academicians from across the country who are dedicated members of the officiating Committee of Medical Disorders in Pregnancy headed by the Federation of Obstetric and Gynaecological Societies of India (FOGSI).

Medical disorders in pregnancy are the diseases which make the pregnancy high risk and are challenging to manage obstetricians and specialists. Many of these diseases may be pre-existing or may develop during pregnancy due to systemic changes associated with pregnancy. Thorough knowledge of approach to management of these high-risk pregnancies associated with medical disorders, is not only important for safe motherhood and child survival but also important for counseling when women take the decisions after understanding the pros and cons of every aspect of modalities available as per the respectful maternity care norms.

The effects of medical disorder and pregnancy are seen peculiarly on each other and may affect the course of the disease and feto maternal outcomes. The purpose of this academic venture is to develop a guiding manual depicting the nuances of evidence-based diagnosis and management of common medical disorders encountered by the obstetricians. The book emphasizes on the role of multidisciplinary role of management and following standard protocols while diagnosing, monitoring and treating these cases. Each topic covers the management of the specific problem from preconception to antenatal care, intrapartum care and postnatal care including guidance on contraception.

Each chapter is penned by highly experienced academicians under the able guidance of Hrishikesh D Pai.

It gives detailed insight into the recent update on management of these high-risk cases.

We hope this book will be a good practical guide for postgraduate students and clinicians practicing obstetrics and gynecology.

Hrishikesh D Pai is the President of FOGSI (2022–2023). He is the Medical Director of Bloom IVF Group and Administrator of FOGSI Manyata Initiative. He is the Director of Corporate Affairs, International Federation of Fertility Societies (IFFS), and adjunct Assistant Professor at Eastern Virginia Medical School, USA. He is a Postgraduate Teacher in gynecology at DNB Examination, India and a Visiting Professor in Obstetrics and Gynecology, Manipal University, India. He has been awarded with the esteemed Fellowship Ad Eundem of the RCOG (Royal College of Obstetricians and Gynaecologists, London, UK). He is the Past Secretary General, Senior Vice President, Deputy Secretary General, Treasurer, and Chairman of FOGSI. He is the Past President of ISAR, IAGE, and MOGS.

Manoj Chellani is the Director of Aayush Hospital and Test Tube Baby Center, Raipur, Chhattisgarh, India. He is the Chairperson of Medical Disorders in Pregnancy Committee, FOGSI (2022–2025). He is an Adjunct Visiting Faculty in Advanced Fertility Program of Department of Obstetrics and Gynecology of Jawaharlal Nehru Medical College (JNMC), Datta Meghe Institute of Higher Education and Research (DMIHER), Wardha, Maharashtra, India. He is the Past President of Raipur Obstetrics and Gynecological Society.

Yashodhara Pradeep is the Vice President of FOGSI (2023). She is the Founder Professor and Head, Department of Obstetrics and Gynecology, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India (Ex). She was the President of Lucknow Obstetrics and Gynecological Society and Chairperson of Family Welfare Committee (2016–2018), FOGSI.

Parikshit Tank is the Treasurer of FOGSI (2021–2024). He is the Senior Consultant Obstetrician and Gynecologist, Ashwini Maternity and Surgical Hospital, Jupiter Hospital, Mumbai, Maharashtra, India. He is the Honorary Professor, Assisted Reproduction, Pacific Medical College and Hospital, Udaipur, Rajasthan, India.

Niranjan Chavan is presently the Professor and Unit Chief at Lokmanya Tilak Municipal General Hospital and Medical College, Sion Hospital, Mumbai, Maharashtra, India. He is holding the position of President MOGS (2022–2023) and Joint Treasurer, FOGSI (2021–2024). He is the Director and Consultant, Chavan Maternity and Nursing Home, Mumbai.

Printed in India

Available at all medical bookstores
or buy online at www.jaypeebrothers.com



JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
OBSTETRICS & GYNECOLOGY

ISBN 978-93-5696-263-7

