THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (January–February 2016) 66(1):10–15
DOI 10.1007/s13224-016-0841-y

INVITED MINI REVIEW

Pregnancy After Cardiac Surgery

Anjali Vivek Kanhere[1] · **Vivek Madhav Kanhere**[2]

Received: 17 October 2015 / Accepted: 9 January 2016 / Published online: 8 February 2016

About the Author

Dr. Anjali Vivek Kanhere is at present Professor of Obstetrics and Gynecology, Chirayu Medical College and Hospital, Bhopal. She is trained in operative endoscopy and medical disorders of pregnancy from Modbury Hospital Adelaide, South Australia. She is associated with Bhopal Obstetrics and Gynecological Society. She is National Corresponding Editor of JOGI.

Abstract Heart disease is one of the common, indirect obstetric causes of maternal death. Management of these cases may challenge the entire team providing care to the mother and fetus. Advances in cardiac surgery has improved quality of life and level of functioning of cardiovascular system of patients with congenital or acquired heart disease. These diseases complicate 0.1–4 % pregnancies. Maternal complications in the form of thromboembolic, hemorrhagic episode and heart failure may occur. The fetus is in danger of effects of oral anticoagulation therapy and other medications given to the patient in order to support cardiovascular system, intrauterine growth restriction and danger of hypoxia. In recent era, we are facing more pregnant patients with previous history of surgical correction of congenital or rheumatic heart disease.

Anjali Vivek Kanhere, MBBS, MD, FICOG FAIMER Fellow (GSMC Mumbai 2011), is a Professor and Head of Department, Department of Obstetrics and Gynecology at Chirayu Medical College and Hospital, Bhopal. Vivek Madhav Kanhere, MBBS, MS, MCh (Cardiothoracic Surgery), is a Consultant and Assistant Professor in Department of Cardiothoracic Surgery at Chirayu Cardiac Center, Chirayu Medical College and Hospital, Bhopal.

✉ Anjali Vivek Kanhere
kanhereanju@yahoo.com

Vivek Madhav Kanhere
kanherevm@yahoo.com

[1] Department of Obstetrics and Gynecology, Chirayu Medical College and Hospital, Bhopal-Indore Highway, Near Bairagarh, Bhopal, Bhopal, MP 462030, India

[2] Department of Cardiothoracic Surgery, Chirayu Cardiac Center, Chirayu Medical College and Hospital, Bhopal, Bhopal-Indore Highway, Near Bairagarh, Bhopal, MP 462030, India

In this review, we have attempted to draw a management protocol of such patients based on the available literature and various international guidelines. In pregnant women with mechanical heart valves, recent data support warfarin use throughout pregnancy, followed by a switch to heparin and planned induction of labor. However, the complexity of this situation demands a cafeteria approach where the patient herself can choose from the available options that are supported by evidence-based information. Preconception counseling, evaluation and antenatal high-risk management protocol with the help of cardiologist and cardiac surgeon improves maternal and neonatal outcome.

Keywords Pregnancy · Cardiac surgery · Anticoagulation · Heparin · Warfarin

Abbreviations

AHA	American Heart Association
ACCP	American College of Chest Physicians
ESC	European Society of Cardiology
INR	International normalized ratio
LMWH	Low molecular weight heparin
UFH	Unfractionated heparin
OAC	Oral anticoagulants

Introduction

Heart disease is one of the most important medical complications during pregnancy. It is one of the common, indirect obstetric causes of maternal death [1]. Approximately 1 % of pregnancies are complicated by cardiac disease. Management of these cases may challenge the entire team providing care to the mother and fetus.

Pregnancy produces a number of alterations in cardiovascular function. The end result of these alterations is increased cardiac work. The demands of pregnancy and heart disease produce lot of stress on the heart.

Advances in cardiac surgery has improved quality of life and level of functioning of cardiovascular system of patients with congenital or acquired heart disease [1]. These diseases complicate 0.1–4 % pregnancies. Management of a pregnant patient after cardiac surgery is a complex issue for all health care providers. It is of extreme challenge for the obstetricians, because both mother and fetus are at risk. Complications resulting in maternal death are thromboembolic, hemorrhagic episode and heart failure [2]. The fetus is in danger of effects of oral anticoagulation therapy and other medications given to the patient in order to support cardiovascular system, intrauterine growth restriction and danger of hypoxia. In recent era, we are facing more patients with previous history of surgical correction of congenital or rheumatic heart disease.

Risk assessment The risk of complications during pregnancy in patients with cardiac surgery depends on the type of surgery, valve prosthesis, anticoagulation status and anticoagulation drugs [3]. It also depends on the patient's symptoms, cardiac function, and her functional capacity.

Patient factors Ideally, these patients are under continuous supervision of the cardiac team. They should be counseled for a planned pregnancy and early reporting of missed periods. Evaluation of pregnancy status with urine pregnancy test and ultrasound confirmation of viable pregnancy along with her obstetric history is must. Evaluation of pregnant women with prosthetic heart valves should include information about her pre-pregnancy functional capacity, ongoing drug treatment, a full clinical assessment and details of valvular prosthesis. A cardiologist evaluation with ECG and an echo cardiology study to evaluate cardiac status will help in risk assessment. There is an increased hemodynamic load during pregnancy, labor and delivery. Patient and her family should be counseled [4] on the high-risk pregnancy status, need of repeated antenatal visits monthly or bimonthly [5] and potential complications that may occur during pregnancy.

Prosthesis-related factors Patients with mechanical valves have increased incidence of thromboembolic events. The commonest cause of maternal death in patients with mechanical heart valves is the device thrombosis.

Drug-related factors Fetal complications related to maternal anticoagulant therapy are teratogenicity and fetal loss. The use of other cardiovascular drugs during pregnancy may also adversely affect the fetal outcome.

Patients who have had, congenital cardiac diseases left-to-right shunt diseases (ASD/VSD/PDA) operated in childhood are seen with pregnancy. If they are operated before onset of significant pulmonary arterial hypertension, they tolerate pregnancy well. Patients who have had tetralogy of Fallot repaired also seem to tolerate pregnancy well; however, if a transannular patch is used, volume overload may cause worsening of pulmonary regurgitation during pregnancy. Patients who have had systemic-pulmonary shunt or palliative procedures should be evaluated to see the functional status of their shunt. These patients still have right-to-left shunt existent; therefore, attendant risk of embolization should be kept in mind.

Valves

Mechanical Mechanical valves are the commonest implanted valves, and thus, patients continue to take oral anticoagulants. If patient opts to switch to UFH, then she should do so under hospital care as chances of valve thrombosis are higher. INR range should be kept around

Table 1 Guidelines for anticoagulation therapy in pregnant women with mechanical heart valves

	ACC/AHA [6]	ACCP [6, 7]	ESC [5, 6]
Oral anticoagulants	Can be used throughout pregnancy, with substitution by dose-adjusted UFH or LMWH during weeks 6–12 of gestation if preferred by the patient	Can be used throughout pregnancy in high-risk[a] patients, with substitution by LMWH or UFH close to term (time frame not specified but normally 48 h before delivery)	If the warfarin dose is ≤5 mg daily, oral anticoagulants throughout pregnancy is the safest regimen (associated with <3 % embryopathy)
Heparin derivatives	Monitored UFH or LMWH might be options throughout gestation or during weeks 6–12 of gestation. LMWH dose should be adjusted to give an antifactor Xa activity 0.7–1.2 U/ml, 4–6 h after administration	Dose-adjusted and monitored LMWH or UFH throughout pregnancy or during weeks 6–12 of gestation is acceptable. In low-risk patients, LMWH should be given twice daily and the dose adjusted to achieve the manufacturer's peak inhibition of factor Xa, 4 h after subcutaneous injection	LMWH or UFH during weeks 6–12 of gestation should be considered if high-dose warfarin is required to maintain therapeutic anticoagulation. LMWH dose should be adjusted to give an antifactor Xa activity of 0.8–1.2 U/ml, 4–6 h after administration
Aspirin	Low-dose aspirin in addition to anticoagulation during the second and third trimesters	Low-dose aspirin in addition to anticoagulation in high-risk[a] patients	Aspirin in addition to anticoagulation is not recommended
Anticoagulation target	INR 3 for all patients with mechanical prosthetic heart valves	INR 2–3 for patients with bileaflet aortic valves without high-risk features[a]	No INR target recommendation

See Jose et al. [8]

ACCP American College of Chest Physicians, *ESC* European Society of Cardiology, *INR* international normalized ratio, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin

[a] First-generation prostheses, mitral valve prostheses, history of thromboembolism, atrial fibrillation, or left ventricular dysfunction

2.5 [6]. If valve thrombosis is suspected, echocardiography is the best diagnostic modality as fluoroscopy involves risks of radiation.

Biological The use of tissue valve prosthesis during childbearing age reduces the risk of thromboembolism and anticoagulation during pregnancy, but is associated with structural valve deterioration (SVD) [7]. It is hastened in patients with bio-prosthesis, and the rate may be higher in mitral position. SVD then exposes the mother to early redo surgery with attended risk and a young child.

Homograft and autograft They are less implanted in our country, but behave the same as bioprosthesis.

Valve Repair

Patients who have had valve repair and are in sinus rhythm are not on oral anticoagulants, but if these patients have had balloon mitral valvuloplasty (BMV), they should be evaluated for their cardiac status with particular emphasis on looking for restenosis or mild regurgitation associated with BMV.

Anticoagulants and Pregnancy

Choice of anticoagulation Oral anticoagulants Coumadin (warfarin) and acenocoumarol (Acitrom) and Heparin Unfractionated Heparin and low molecular weight heparin LMWH [8] Table 1.

Oral anticoagulants Coumadin (warfarin) was approved for the use in 1960s and became the most widely prescribed OAC drug. Vitamin K antagonists (VKA) such as phenprocoumon or acenocoumarol (Acitrom) differ mainly in their half-life. Warfarin, a coumarin derivative, classical vitamin K receptor antagonist is a low molecular weight oral anticoagulant which has been in clinical use for 50 years. It is a difficult drug to use, with a narrow therapeutic index comes in many tablet strengths: 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg. Initiation of warfarin at a dose of 4–5 mg daily is recommended. The advantage of warfarin lies in its ease of administration, dependability and low cost. Acitrom is similar to warfarin but with longer half-life and lesser interactions. It is available as 1-, 2- and 4-mg tablets. Dosage is adjusted to attain a desired international normalized ratio (INR) level of 2.5–3.5 [4, 9].

Heparin Heparin is a naturally occurring anticoagulant produced by basophils and mast cells. Unfractionated heparin as a pharmaceutical is heparin that has not been fractionated to sequester the fraction of molecules with low molecular weight. In contrast, low molecular weight heparin has undergone fractionation for the purpose of making its pharmacodynamics more predictable. Heparin (both UFH and LMWH) does not cross the placenta and does not cause teratogenicity.

Unfractionated heparin Measuring activated partial thromboplastin time (aPTT) remains the most frequently used method for monitoring the anticoagulant response of unfractionated heparin (UFH) and should be measured

about 6 h after the bolus dose. Long-term heparin therapy may cause osteoporosis and thrombocytopenia.

LMWH LMWH has a better bioavailability and has a lower risk of bleeding, thrombocytopenia and osteoporosis, but has a longer half-life. In 2004, it was rephrased that its use for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied.

Aspirin Aspirin reduces the incidence of systemic embolization, and 80-100 mg of aspirin during the second and third trimesters may be added to improve antithrombotic effects.

Decisions on the choice of anticoagulation should be made by both physicians and patient [10]. The American College of Cardiology/American Heart Association Task Force on Practice Guidelines for the Management of Patients with Valvular Heart Disease: 2014 recommendations are the use of warfarin and then UFH in anticipation of labor.

Special Consideration

Heart failure The increased physiologic demands of pregnancy (increased blood volume and cardiac output) may result in the development or exacerbation of heart failure in patients with ventricular dysfunction or dysfunction of native or prosthetic valves.

Embryopathy Warfarin readily crosses the placenta. Vitamin K acts as a cofactor for carboxylation of glutamic acid residues of osteocalcin and matrix Gla protein, which modulate calcium deposition. Oral anticoagulants when used during the first trimester may thus cause a failure in the synthesis of osteocalcin and Gla matrix protein resulting in nasal hypoplasia and stippling seen on X-ray of proximal epiphyseal growth areas (chondroplasia punctata). Exposure during the second and third trimesters may lead to central nervous system and eye abnormalities (optic atrophy, cataract, blindness, microphthalmia, intraventricular hemorrhage, microcephaly, hydrocephalus, seizures and growth/mental retardation) [11]. The greatest susceptible period for developing warfarin embryopathy is between the sixth to ninth weeks of gestation. Incidence of coumarin embryopathy is a subject of intense debate. A close relationship between warfarin dose and fetal complications is reported.

Fetal loss Spontaneous abortion is by far the most frequent fetal complication, associated with pregnancy in women with mechanical heart valves.

Embolic complications Pregnancy is associated with an increased incidence of thromboembolism due to hypercoagulable state.

Maternal bleeding complications The overall rate of major bleeding in pregnant females with mechanical heart valves was reported to be 2.5 % [12]. This risk is similar in either heparin or warfarin therapy. Warfarin should preferably be substituted with heparin at 35–36 gestational weeks to avert bleeding accidents during delivery, with planned induction of labor or cesarean section at 38 weeks.

Breast feeding Warfarin does not causes an anticoagulant effect on the breast-fed infant. Neither UFH nor LMWHs are secreted into breast milk.

Management Plan

Role of termination Pregnancy is generally not recommended when the patient is in functional class 3 or 4 on the NYHA. If termination of pregnancy is needed in view of diagnosed missed abortion, whether a surgical approach is safer than the medical one is not very clear as the evidence is scarce [13]. The surgical approach is preferred as it allows the procedure to be performed in a more scheduled manner to obtain the best outcome. Surgical termination has a relatively short duration and reduced risk of failure, and the anesthetic risk can be minimized using a general anesthesia [14]. Oxytocics can be used cautiously, and endocarditis prophylaxis though is not recommended is advised in the Indian scenario. Medical termination of pregnancy seems to be more risky due to pain, severe hemorrhage, time taken and risk of failure [15].

Obstetric and neonatal issues There is an increased risk of preterm labor, postpartum hemorrhage, operative deliveries and postoperative hematoma formation. Neonates are at risk of prematurity, intracranial hemorrhage and warfarin embryopathy.

Anticoagulation Issues

Candidates for anticoagulation treatment For patients with mechanical heart valve, lifelong anticoagulation is mandatory [16]. The state of hypercoagulability extends into the postpartum period too and requires a persistently higher maintenance dose of OAC.

How anticoagulation therapy should be administered [10] Table 2

How should it be monitored? The prothrombin time (PT) [6] is the laboratory test of choice for monitoring the anticoagulation status of patients treated with oral anticoagulants. Standardization of the prothrombin time (PT) with the international normalized ratio (INR) allows for

Table 2 Nishimura et al. [10] AHA/ACC valvular heart disease guideline

Class I	1. Therapeutic anticoagulation with frequent monitoring is recommended for all pregnant patients with a mechanical prosthesis	(Level of evidence: B)
	2. Warfarin is recommended in pregnant patients with a mechanical prosthesis to achieve a therapeutic INR in the second and third trimesters	(Level of evidence: B)
	3. Discontinuation of warfarin with initiation of intravenous UFH [with an activated partial thromboplastin time (aPTT) >2 times control] is recommended before planned vaginal delivery in pregnant patients with a mechanical prosthesis	(Level of evidence: C)
	4. Low-dose aspirin (75–100 mg) once per day is recommended for pregnant patients in the second and third trimesters with either a mechanical prosthesis or bioprosthesis	(Level of evidence: C)
Class IIa	1. Continuation of warfarin during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is 5 mg per day or less after full discussion with the patient about risks and benefits	(Level of evidence: B)
	2. Dose-adjusted LMWH at least 2 times per day (with a target antiXa level of 0.8–1.2 U/ml, 4–6 h postdose) during the first trimester is reasonable for pregnant patients with if the dose of warfarin is >5 mg per day to achieve a therapeutic INR	(Level of evidence: B)
	3. Dose-adjusted continuous intravenous UFH (with an aPTT at least 2 times control) during the first trimester is reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is >5 mg per day to achieve a therapeutic INR	(Level of evidence: B)
Class IIb	1. Dose-adjusted LMWH at least 2 times per day (with a target antiXa level of 0.8–1.2 U/ml, 4–6 h postdose) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg per day or less to achieve a therapeutic INR	(Level of evidence: B)
	2. Dose-adjusted continuous infusion of UFH (with aPTT at least 2 times control) during the first trimester may be reasonable for pregnant patients with a mechanical prosthesis if the dose of warfarin is 5 mg per day or less to achieve a therapeutic INR	(Level of evidence: B)
Class III: harm	LMWH should not be administered to pregnant patients with mechanical prostheses unless antiXa levels are monitored 4–6 h after administration	(Level of evidence: B)

uniform measurement of the anticoagulation status of patients on oral anticoagulants. Frequency of monitoring: initiation phase 4–5 times per week, stable phase: once each 4 weeks. Transition phase: more close monitoring, concurrent heparin therapy: INR estimation can lead to over-estimation of the therapeutic level of oral anticoagulation, close monitoring is advised.

The anticoagulation effect of UH can be reliably monitored by the activated partial thromboplastin time (aPTT), which is a widely available test. However, the anticoagulation effect of LMWH is not reflected by the aPTT. Assessment of LMWH activity requires assessment of the antifactor Xa level, a test that is not universally available.

Management at the time of delivery Stop warfarin at the 36th week, replacing it with adequate heparin and planned induction of labor at 38th week [3].

Issues in oral anticoagulant therapy peculiar to India Indians with their low body weight and body mass index (BMI) require lesser doses of OAC, and different dietary habits make them more prone for warfarin–food interactions. Usage of over-the-counter medications (NSAIDS) increases the action of OAC [17]. Monitoring of warfarin therapy with standardized measurement of prothrombin time (PT)/INR poses a practical problem.

Resume anticoagulation treatment A reasonable approach to minimize bleeding complications is to restart unfractionated heparin or LMWH no sooner than 4–6 h after vaginal delivery or 6–12 h after cesarean delivery, followed by starting OAC as soon as possible.

Endocarditis prophylaxis Antibiotic prophylaxis is the mainstay of prevention and needs to be adjusted to the type of procedure which the patient is about to undergo. Prophylaxis should be directed mainly against *Enterococcus faecalis*, using ampicillin 2G intravenously plus gentamycin 80 mg 30 min before starting the procedure with a second dose 6 h after the procedure is recommended.

Other medication The use of other cardiovascular drugs during pregnancy may also adversely affect the fetal outcome. Cardiac drugs that are relatively safe during pregnancy include heparin, propranolol (and other beta blockers), verapamil, digoxin and few antihypertensive such as labetalol, methyldopa, hydralazine and nifedipine.

Diuretics They are not teratogenic. Diuretics do affect the plasma volume expansion of normal pregnancy, and this has not been correlated with a negative effect on fetal growth [18].

Management of valve thrombosis during pregnancy
Heparin may be considered for small, nonobstructive thrombi. However, for obstructive valve thrombosis, the

treatment options are surgical intervention and thrombolysis, both of which carry substantial fetal and maternal risks.

Mode of delivery Delivery should be planned, and its modality discussed in close collaboration with the obstetricians, cardiologists, anesthesiologists and pediatrician. Planned inductions or cesarean deliveries are necessary for transition and management of anticoagulants [3]. Vaginal delivery is preferred in most cases, and cesarean delivery should be reserved for specific obstetrical indications. On rare occasions, urgent delivery is necessary for a woman with a mechanical valve while she is still receiving therapeutic anticoagulation [19]. Management involves balancing the risk of life-threatening maternal hemorrhage against the potentially catastrophic risk of thromboembolism or valve thrombosis.

Contraceptive advice Contraception counseling is an important aspect of care. Progesterone-only forms of contraception [20], IUDs, barrier methods and COCs are the alternatives.

Our approach Management of pregnant women with cardiac surgery requires special clinical expertise and collaborative management by the cardiac surgeon, cardiologist, obstetrician, and anesthetist. Patients should be informed fully about the maternal and fetal risks associated and importance of therapeutic anticoagulation throughout pregnancy.

Inference In today's litigation-riddled environs, the decision on whether to replace warfarin with heparin between 6 and 12 weeks of gestation or to continue with warfarin throughout pregnancy should be made after full discussion with the mother, her partner and family members. However, warfarin should preferably be substituted with heparin at 35–36 gestational weeks to avert bleeding accidents during delivery, with planned induction of labor or cesarean section at 38 weeks.

Conclusions

Counseling, compliance, cost factors, tender loving care and effective team work is the first line of treatment in pregnant patients with cardiac surgery.

Compliance with Ethical Standards

Conflict of interest The author has no conflict of interest.

References

1. Royal College of Obstetricians and Gynaecologists. Why mothers die 2000–2002—the sixth report of confidential enquiries into maternal deaths in the United Kingdom. London: RCOG press; 2004.
2. Plesinac S, Pilic I. Course and outcome of pregnancy after the heart surgery. In: Proceedings of the world medical conference Prague. September 2011.
3. Srivastava AP, Modi P, Sahi S, et al. Anticoagulation for pregnant patients. Ann Card Anesth. 2007;10:95–107.
4. Elkayam U, Bitar F. Valvular heart disease and pregnancy part II: prosthetic valves. J Am Coll Cardiol. 2005;46(3):403–10. doi: 10.1016/j.jacc.2005.02.087.
5. European Society of Gynecology (ESG), Association for European Pediatrics Cardiology (AEPC), German Society for Gender Medicine (DGesGM), et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147.
6. Hirsh J, Dalen JE, Deykin D et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. In: Fourth ACCP consensus conference on antithrombotic therapy. Chest. 1995; 108(suppl):231S–246S.
7. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy clinical update. Circulation. 2003;107:1240–6.
8. Castellano JM, Narayan RL, Vaishnava P, et al. Anticoagulation during pregnancy in patients with a prosthetic heart valve. Nat Rev Cardiol. 2012;9:415–24. doi:10.1038/nrcardio.2012.69.
9. James A. Committee on practice bulletins—obstetrics. Thromboembolism Pregnancy Obstet Gynecol. 2011;118(3):718–29. doi:10.1097/AOG.0b013e3182310c4c.
10. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:e57.
11. Starling LD. Fetal warfarin syndrome. BMJ Case Reports http://casereports.bmj.com/content/2012/bcr-2012-007344.
12. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systemic review of the literature. Arch Intern Med. 2000;160:191–6.
13. Sorin C. Juverdeanu surgical termination of pregnancy for maternal cardiac disease: a safer option? TMJ. 2009;59(2):169–72.
14. Ray P, Murphy GJ. Recognition and management of maternal cardiac disease in pregnancy. Br J Anaesth. 2004;93(3):428–39.
15. Gary M, Harrison J. Analysis of severe adverse events related to the use of mifepristone as an abortifacient. Ann Pharmacother. 2006;40(2):191–7.
16. Bonow RO, Carabello BA, Chatterjee K et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008;118(15):e523–661.
17. Gopalakrishnan S, Narayanan S. Oral anticoagulants: current Indian scenario. In: Medicine update. The Association of Physicians of India; 2013. p. 410–3.
18. Sibai BM. Effects of diuretics on plasma volume in pregnancies with long-term hypertension. Am J Obstet Gynecol. 1984;150(7):831–5.
19. North RA, Hunt B, Gaasch WH et al. Management of pregnant women with prosthetic heart valves, 2015.
20. Silversides CK. Choosing the best contraceptive method for the adult with congenital heart disease. Curr Cardiol Rep. 2009;11:298–305.