

# Palpitation Profile in Pregnant Ladies in Mosul City

Hana Abdul-QaderKhuder<sup>1</sup>, Dalya Mudhafar Abdulrahman<sup>2</sup>, Saba Abdulateef Mahmood<sup>3</sup>

<sup>1,2</sup>College of medicine/ Ninevah University, Mosul, Iraq

<sup>3</sup>DGO, Ministry of Health, Alsalam Teaching hospital, Mosul, Iraq

# ABSTRACT

Increased heart rate is a normal physiological adaptation occurring during pregnancy. Some women have severe tachycardia requiring medical attention. Palpitation is common and often frightening for the pregnant women, but is usually benign.

The pregnant patient with arrhythmias most often seeks medical attention because of palpitations, lightheadedness, shortness of breath and anxiety. Arrhythmias occurring during pregnancy can cause significant symptoms and even death in mother and fetus. The management of these arrhythmias is complicated by the need to avoid harm to the fetus and neonate. Management of arrhythmias in pregnant women is similar to that in non- pregnant but a special consideration must be given to avoid adverse fetal effects.

Certain drugs may cross the placental barrier; such the careful consideration should be given in selecting the anti-arrhythmic drug to prevent adverse effects on the fetus.

Keywords: Palpitation, Arrhythmia, Pregnancy.

## INTRODUCTION

Pregnancy is characterized by several and reversible changes in cardiovascular system to meet the increased demands of both mother and fetus. Increased heart rate is a normal physiological adaptation occurring during pregnancy<sup>(1)</sup>.

Normal pregnancy is characterized by increased cardiac output by approximately 50% due to an increase in stroke volume as a result of reduced vascular resistance and an increase in blood volume, The heart rate rises by 10–20 beats per minute, mainly during the third trimester<sup>(2,3)</sup>.

Palpitation is a common symptom during pregnancyandare usually benign, These palpitations can be severe enough to affect the daily activity of pregnant women<sup>(3,4)</sup>.

A few women presenting with palpitations will have significant cardiac arrhythmias, which are the most common heart complication in pregnancy<sup>(5)</sup>. About 50% of pregnant women who are investigated for palpitations are found to have ectopic beats or non-sustained arrhythmias<sup>(6)</sup>.

Arrhythmias in pregnancy are common and can cause concern for the wellbeing of both the mother and the fetus. For some mothers the arrhythmias may be a recurrence of a previously diagnosed arrhythmia or the first presentation in a woman with known structural heart disease. In most cases, however, there is no previous history of heart disease, and the new occurrence of a cardiac problem can generate considerable anxiety<sup>(7)</sup>.

The management of arrhythmias is determined by the need to avoid harm to the fetus and neonate. It is useful to classify patients with arrhythmias into those with and without structural heart disease<sup>(8)</sup></sup>.

## Arrhythmogenesis

The generation of arrhythmias in pregnancy may be related to a combination of haemodynamic, autonomic and hormonal factors. An increase in atrial and ventricular stretch that is secondary to an increased blood volume may contribute. Higher levels of estrogen may increase alpha-adrenergic receptors, resulting in an enhanced adrenergic response<sup>(9,10)</sup>.



## Electrocardiogram changes

A resting 12-lead electrocardiogram (ECG) in pregnancy will demonstrate an increase in heart rate. There may be a slight left axis deviation, within the normal range, which is due to the rotation of the heart from the gravid uterus<sup>(8)</sup>. Inverted or flattened T waves in leads III, V1–V3 and a Q wave in leads II, III and aVF, are also commonly seen<sup>(15)</sup>. Atrial and ventricular ectopic beats are also more frequent; 50–60% of pregnant women will have ectopic beats on continuous ECG recordings<sup>(6)</sup>.

#### Examination

Basic observations – including a manual palpation of the pulse, blood pressure, respiratory rate, oxygen saturation and temperature – are essential, both in the acute and non-acute presentation. Cardiovascular examination, including auscultation of the heart, will elicit any abnormal heart sounds that raise the possibility of underlying heart disease. Although a flow murmur is a common finding in pregnancy, in the context of a presentation with cardiac symptoms, further investigation for structural heart disease is important<sup>(3)</sup>.

#### **Management of palpitations**

#### Definitions

Palpitations are defined as an unpleasant awareness of the heartbeat<sup>(11)</sup>. The sensation of the heart beating may be forceful, irregular or fast. Under normal conditions, the heartbeat is not usually realized <sup>(12)</sup>. However, during exercise or at times of emotional stress, it is normal for the individual to become aware of their heart beating. Ingestion of substances such as coffee and nicotine, which increase adrenergic tone, can also have the same effect, inducing a symptomatic sinus tachycardia.<sup>(11,12)</sup>.

In these cases, palpitations are considered physiological rather than pathological. During pregnancy, women may experience the sensation of a 'pounding heartbeat', originating from a heightened awareness of the physiological increase in heart rate and accompanying increased stroke volume<sup>(8)</sup>. Atrial and ventricular ectopic beats are often experienced as a 'missed' or 'skipping' heartbeat. Many women presenting with palpitations will be experiencing an awareness of these benign, physiological changes rather than a pathological arrhythmia.(Table <u>1</u>) summaries the differential diagnoses of palpitations in pregnancy.

Aetiology	Diagnosis				
Physiological/	Relative sinus tachycardia of pregnancy				
benign	Exercise or stress-induced sinus tachycardia				
	Occasional ectopic beats				
Arrhythmias	Supraventricular tachycardia/extrasystoles				
	Atrial fibrillation/flutter				
	Ventricular tachycardia/extrasystoles				
	Bradyarrhythmias: sinus bradycardia, atrioventricular heart block				
Systemic	Hyperthyroidism				
causes	Anaemia				
	Sepsis				
	Hypovolaemia				
	Pulmonary embolus				
	Hypoglycaemia				
	Phaeochromocytoma				
	Postural orthostatic tachycardia syndrome (POTS)				

## Table 1. Differential diagnosis of palpitations in pregnancy<sup>(3)</sup>

#### **Risk Factors for Palpitations During Pregnancy**<sup>(13)</sup>

The Many factors can increase a person's cardiovascular risk of having heart palpitations during pregnancy. Those include:

- Age, particularly if 35 years or older when pregnant.
- Existing heart defects.
- Cardiomyopathy, a disease that makes it harder for the heart to pump blood.
- Family health history, like a parent or close relative who has an arrhythmia.
- Lifestyle habits, including drinking, smoking or using drugs such as cocaine.
- Preexisting high blood pressure or the development of high blood pressure during pregnancy, aka preeclampsia.



- Diabetes or low blood sugar.
- Autoimmune disorders like lupus.
- Obesity.
- Other medical conditions, ranging from flu to sleep apnea.

Women with congenital heart disease are particularly at risk of a pathological arrhythmia, especially those who have previously had cardiac surgery(7,14). It should also be borne in mind that underlying cardiac conditions can present for the first time in pregnancy.

#### Table 2: Summarizes the Clinical Features That Might Raise Suspicion of an Arrhythmia<sup>(3)</sup>

Reassuring features	Features requiring further attention		
Awareness of a fast, regular heartbeat, particularly	Fast and irregular heart beat		
when lying down			
Occasional 'thumping sensation' suggestive of	Palpitations waking from sleep or at work		
occasional ectopic beats			
Pre-vasovagal symptoms preceding the palpitations	Dizziness following the onset of palpitations		
	Shortness of breath, chest pain, syncope		
	Associated headache, sweating or abdominal pain and/or		
	hypertension (consider phaeochromocytoma)		
	Personal history of pre-existing cardiac disease		
	Family history of cardiac disease, e.g. long QT syndrome,		
	cardiomyopathy, sudden death		

#### Lifestyle Changes to Reduce Palpitations<sup>(13)</sup>

Define abbreviations and acronyms the first time they are used in the text, even after they have been defined in the abstract. Abbreviations such as IEEE, SI, MKS, CGS, sc, dc, and rms do not have to be defined. Do not use abbreviations in the title or heads unless they are unavoidable.

Experts say for those who never experienced heart palpitations before pregnancy and where there's no serious underlying cause, the palpitations often resolve on their own.

Even so, clinicians say it's important to determine risk factors whenever possible. That includes stop smoking, illicit drugs of any kind and alcohol consumption during pregnancy. "There is no known safe amount of alcohol during pregnancy or when trying to get pregnant," according to the Centers for Disease Control and Prevention. Also, ensure that other health conditions like diabetes and high blood pressure are well-controlled

Additionally, these lifestyle changes may also help reduce palpitations:

- Stay well hydrated.
- Avoid heavy meals, instead opting for more frequent, smaller meals.
- Do everything you can to get adequate rest.
- Limit caffeine intake.
- Exercise regularly.
- Manage stress and anxiety with meditative activities like yoga.

#### Investigation 12-lead electrocardiogram

Although pregnant women often report palpitations to their doctor, the doctor is usually not present during a symptomatic episode of palpitations when the 12-lead ECG is the gold standard for diagnosis<sup>(12)</sup>. Occasionally, if women have been seen in an emergency unit, a copy of an ECG taken at the time may be available.

An abnormal baseline ECG may indicate underlying pathology and is therefore an essential part of arrhythmia assessment. For example, the ECG of a woman with Wolff-Parkinson-White syndrome may show a delta wave; high voltages in the precordial leads with Q wave and ST changes may be seen in hypertrophic cardiomyopathy, or a corrected QT interval of more than 460 ms in long QT syndrome (LQTS)<sup>(7,12)</sup>. Any variant other than those already described as normal changes in pregnancy should prompt a second opinion from a cardiologist.

#### Echocardiogram

An echocardiogram will exclude structural heart disease and is an important investigation in the assessment of palpitations in many pregnant women. In pregnant women for whom the clinician believes symptoms are physiological rather than pathological, an echocardiogram may not be required. Table <u>3</u> summarises the types of patients who might need an echocardiogram.



## Table 3. Who needs an echocardiogram?<sup>(3)</sup>

Features suggesting need for echocardiogram	Echocardiogram may not be indicated		
Diagnosed arrhythmia	Symptoms consistent with physiological changes in pregnancy		
Audible heart murmur	Isolated sinus tachycardia at time of symptoms on ambulatory		
	ECG		
Concerning features on history, e.g. shortness of breath	Infrequent ectopic beats in the absence of other signs of		
	structural heart disease/inherited arrhythmia		
Known structural heart disease			
Previous chemotherapy with cardiotoxic agents			
Family history of inherited arrhythmia, e.g. long QT			
syndrome, sudden cardiac death			

• ECG = electrocardiogram.

## Long QT syndrome

LQTS is characterised by a prolonged QT interval on the ECG, secondary to a disorder of ventricular myocardial repolarization. This can lead to ventricular arrhythmias, typically torsade de pointes and a risk of sudden death. Events appear to be less common during pregnancy, but women should remain on beta blocker therapy throughout and most importantly after pregnancy<sup>(31)</sup>.

## Management of pregnancy in pre-existing arrhythmia

Ideally, women with a pre-existing cardiac arrhythmia should be managed by a multidisciplinary team, which should include an obstetrician with an interest in maternal medicine, a cardiologist and an anaesthetist. Care will vary depending on the condition and any associated underlying cardiac disease. Box <u>3</u> summarises the general principles of management.

## Box 3. General principles of the management of pre-existing arrhythmias.

#### Preconception

- Condition-specific advice on risk in pregnancy
- Review of medication and changes advised if appropriate
- Optimisation of condition prior to conceiving; consider referral for accessory pathway ablation

## Antenatal

- Review of medication
- Growth scans if on beta-blockers
- Anaesthetic review and planning
- Planning for birth

## Intrapartum

- Vaginal birth usually recommended
- Consider place of birth if risk of arrhythmia high; co-located unit with appropriate facilities
- Consider continuous cardiac monitoring in those at high risk
- Care plan to include advice on management of acute arrhythmia and ensure drugs/facilities available in advance, and drugs to be avoided

## Postnatal

- Period of inpatient monitoring
- Some conditions high risk of postnatal event, e.g. long QT syndrome
- Plans for medication and breastfeeding
- Ensure plans for continuing cardiological care/investigations arranged

## PATIENTS AND METHOD

AfterIt is a randomized control trial involve two hundred pregnant ladies .This study done among pregnant women that came to our private clinic for their complains of palpitation, done in Mosul city from the period of 5<sup>th</sup> of February 2020 till 25<sup>th</sup> of April 2020. The methodology of this study applied in this study involves direct questioning using questionnaires, and in addition to clinical assessment of the patients.

Information on age, education, parity, occupation, obstetric, medical and surgical history was obtained from the women using a close ended questionnaire.



All females involve in our study as volunteers will received compensation for what is going on, plan how we examine her, who to manage which mean related medical care, follow up we start from physical examination, laboratory test and all female with no any coasty embarrassment. All female under ethical consideration at whole time of study and consents taken from all.

Inclusion and exclusion criteria planed and the strategy of study put, so the inclusion data involved: pregnant ladies, from 20 to 45 years, BMI from 18 to 24, parity, residence, their social habit for smoking and bathing, drugs and medical history taken. For exclusion data: not pregnant ladies, those with known cardiac or thyroid disease, anemic ladies, ill and febrile pregnant ladies, and using of drugs could effect on heart rate.

## Sample size collection and data collection:

Two hundred pregnant ladies included in our study, all randomly collected, we invited female with inclusion and exclusion criteria discuss with them the value that they gain.

For data collection we involved social demographic characteristic features of female. Life style habits as smoking, routine daily practice as how many time and numbers of cup of tea and coffee they take every days, how they can do deal with such problem if they do have it as some ladies stop any hard work other increase daily intake of water.

**Physical examination:** any female involve in study we examine for pulse rate, blood pressure, and temperature. Thyroid gland examination and any signs of anemia include in examination for consideration could patients have thyroid and/or anemia and they didn't know. Electrocardiogram and Echo study also send these ladies to exclude cardiac disease.

## Laboratory investigation:

The blood samples collected from the pregnant ladies and we send to examination for thyroid function test and hemoglobin percentage to exclude both thyroid diseases and anemia.

## Data analysis:

Chi square test with P value of < 0.05 were the value significant statically. Score that obtained involved follow up of 200 pregnant female divided in to groups one life styles changes, medical treatment including anxiolytic, Inderal or concor and mixed group those use medical drug and life style changes. The treatment was given to medical and mixed groups, the life style changes group based on their changes in daily life.

The text edit has been completed, the paper is ready for the template. Duplicate the template file by using the Save As command, and use the naming convention prescribed by your conference for the name of your paper. In this newly created file, highlight all of the contents and import your prepared text file. You are now ready to style your paper; use the scroll down window on the left of the MS Word Formatting toolbar.

## RESULTS

Two hundred pregnant ladies were randomly collected from our private clinic complaint from palpitation, some use life style changes method, other used anxiolytics and medical management methods and followed them in the next antenatal visits to examine for the effectiveness of the management method use.

(Table 5) and (fig, 1) show the comparison between different method of managements use to control palpitation in two hundred pregnant ladies and the correlation was found significant between the use of Inderal 5 mg and control of palpitation as the P value was < 0.001.

#### Table 5 : Shows comparison between different method of managements use to control palpitation in two hundred pregnant ladies

Treatment	Case no.	%	Chi <sup>2</sup>	P-value
Anoxyliticdrug	3	2.13	61.79	0.0001**
Concor (10mg) only	3	2.13		
Concor (10mg) with life style	3	2.13		
Concor (5mg) only	12	8.51		
Concor (5mg) with life	24	17.02		
inderal (10mg) only	24	17.02		
inderal (10mg) with life style	18	12.77		
inderal (5mg) only	33	23.4		
inderal (5mg) with life	21	14.89		
Total	141	100%		

\*\* a high significant differences between treatment according to chi<sup>2</sup> test.





Figure 1: different method and drugs use for control of palpitation in 200 pregnant ladies.

# DISCUSSION

Pregnancy may be associated with various types of ventricular and supraventricular arrhythmias. Ideally, management should start before conception, but during pregnancy treatment should only be initiated for severe symptoms or hemodynamic compromise.

In general, arrhythmias during pregnancy can be safely managed medically with little risk to mother or fetus. Drugs should be avoided in the first trimester if possible and the choice of drug should reflect its safety record in pregnancy as well as the particular arrhythmia being treated and any associated structural heart disease. Drugs should be administered in the lowest effective dose and the mother and fetus monitored carefully throughout the pregnancy.

In emergency situations, or where medical treatment has failed, DC cardioversion can be safely administered throughout pregnancy. Cardiac arrest is rare; however, the physician should be aware of special circumstances that need to be considered [32].

Data evaluating the use of medications to control symptomatic benign palpitation in pregnant women are limited. Increased heart rate is a normal physiological adaptation occurring in pregnancy. Many pregnant women would be able to tolerate it. However, some of them would have severe tachycardia requiring medical attention and intervention. In our study, we found that only about 25% of pregnant women with symptomatic tachycardia or palpitation receive treatment, despite the available evidence of the safety of drugs being used [33,34]. Drugs commonly used are rate control medications, which include Beta- blockers, calcium channel blockers and other antiarrhythmic agents like digoxin. Propranolol, one of the commonest Beta-blockers, which is used during pregnancy for maternal and fetal indications, has been shown not to be teratogenic. Verapamil, which is used as an antiarrhythmic agent, has also been shown to have a very low risk or nonexistent risk when used in any portion of pregnancy. Digoxin has no teratogenic effect and pregnancy recommendations show compatibility [35]. In our study, all women who were given treatment reported resolution of their symptoms, ability to perform their activities of daily living [1].

# CONCLUSION

Palpitation in pregnancy is a common complaint in pregnancy. However, only a small number of patients receive treatment despite the safety of drugs that are used to control symptomatic tachycardia. The number of patients in our study is small and therefore, further larger studies are needed to evaluate the management of symptomatic benign palpitation in pregnancy.



#### REFERENCES

- [1]. E.Al-Yaseen, , A.Al-Na'ar, , M.Hassan, G.Al-Ostad, and Ibrahim, E., "Palpitation in pregnancy: experience in one major hospital in Kuwait", Medical journal of the Islamic Republic of Iran, 2013, 27(1), p.31.
- [2]. J.L. Merino, A.Perez-Silva, "Tachyarrhythmias and pregnancy". EJ Cardiol Prac, 2011, Vol. 9, p.31.
- [3]. A.Roberts, J.Mechery, A. Mechery, B.Clarke, and S.Vause, Management of palpitations and cardiac arrhythmias in pregnancy. The Obstetrician & Gynaecologist, 2019. 21(4), pp.263-270.
- [4]. AC.Van Oppen, RH.Stigter, HW.Bruinse Cardiac output in normal pregnancy: a critical review. Obstet Gynecol. 1996;87(2):310.
- [5]. W.Drenthen, E.Boersma, A.Balci, P.Moons, Roos-Hesselink JW, Mulder BJ, Vliegen HW, van Dijk AP, Voors AA, Yap SC, van Veldhuisen DJ, Pieper PG. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 2010; 31: 2124–32.
- [6]. A.Shotan, E.Ostrzega, A.Mehra, J.V. Johnson, and U.Elkayam, Incidence of arrhythmias in normal pregnancy and relation to palpitations, dizziness, and syncope. The American journal of cardiology, 1997, 79(8), pp.1061-1064.
- [7]. D. L.Adamson, &C.Nelson-Piercy, Managing palpitations and arrhythmias during pregnancy. Postgraduate medical journal, 2008, 84(988), p. 66-72.
- [8]. R. Cordina, and M.A.McGuire, Maternal cardiac arrhythmias during pregnancy and lactation. *Obstetric medicine*, 2010, *3*(1), pp.8-16.
- [9]. JP.Greenwood, EM.Scott, JB.Stoker, JJ.Walker, DA.Mary, Sympathetic neural mechanisms in normal and hypertensive pregnancy in humans. Circulation 2001; 104: 2200–4.
- [10]. JM.Roberts, PA.Insel, A.Goldfien. Regulation of myometrial adrenoreceptors and adrenergic response by sex steroids. Mol Pharmacol 1981; 20: 52–8.
- [11]. P.Brugada, S.Gürsoy, J.Brugada, E.Andries, Investigation of palpitations. Lancet 1993; 15( 341): 1254-8.
- [12]. A.Raviele, F.Giada, L.Bergfeldt, JJ.Blanc, C.Blomstrom Lundqvist, Mont L, et al. Management of patients with palpitations: a position paper from the European Heart Rhythm Association. Europace 2011; 13: 920- 34.
- [13]. Are Heart Palpitations During Pregnancy Cause for Concern? Nathaniel Smilowitz; Adam Lewkowitz; Evelina Grayver, MD.
- [14]. F.Neuberger, C. Nelson Piercy, Acute presentation of the pregnant patient. Clin Med 2015; 15: 372-6.
- [15]. Sunitha M, Chandrasekharappa S, Brid S. Electrocardiographic Qrs axis, Q wave and T wave changes in 2nd and 3rd trimester of normal pregnancy. J Clin Diagn Res 2014; 8: 17-21.
- [16]. P.Thavendiranathan, A.Bagai, C.Khoo, P.Dorian, NK.Choudhry, Does this patient with palpitations have a cardiac arrhythmia? JAMA 2009; 302: 2135–43.
- [17]. AA.Mahendru, TR.Everett, IB.Wilkinson, CC.Lees, CM. McEniery. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. J Hypertens 2014; 32: 849–56.
- [18]. PK.Stein, MT. Hagley, PL, Cole, PP. Domitrovich, RE. Kleiger, JN. Rottman, Changes in 24 hour heart rate variability during normal pregnancy. Am J Obstet Gynecol 1999; 180: 978 - 85.
- [19]. M. Tawam, J. Levine, M.Mendelson, J.Goldberger, A.Dyer, A.Kadish, "Effect of pregnancy on paroxysmal supraventricular tachycardia. Am J Cardiol 1993; 72: 838–40.
- [20]. SH.Lee, SA.Wu TJ,Chen,CE. Chiang CCCheng, CT. Tai et al., "Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. Am J Cardiol 1995; 76: 675–8.
- [21]. Di Biase L, Walsh EL. Wolff Parkinson "White syndrome: anatomy, epidemiology, clinical manifestations, and diagnosis. In: S Lévy, BP Knight, BC Downey, eds. UpToDate. Waltham, MA: Wolters Kluwer; 2018
- [22]. JM. Miller, "Therapy of Wolff Parkinson White syndrome and concealed bypass tracts: Part I. J Cardiovasc Electrophysiol 1996; 7: 85-93.
- [23]. C.Silversides, L.Harris, S C. Yap, Supraventricular arrhythmias during pregnancy. In: H Calkins, NAM Estes, BC Downey, eds. UpToDate. Waltham, MA: Wolters Kluwer; 2018 [https://www.uptodate.com/contents/supraventricular-arrhythmiasduring-pregnancy].
- [24]. U.Elkayam, TM.Goodwin, Jr. Adenosine therapy for supraventricular tachycardia during pregnancy. Am J Cardiol 1995; 75: 521–3.
- [25]. RL.Page, JA.Joglar, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2016; 67: e27–115.
- [26]. Regitz Zagrosek V, Roos Hesselink JW, Bauersachs J, Blomström Lundqvist C, Cífková R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018; 39: 3165 - 241.
- [27]. R.Phang, JM.Prutkin, LI. Ganz Overview of atrial flutter. In: PG Zimetbaum, GM Saperia, eds.UpToDate. Waltham, MA: Wolters Kluwer; 2017 [https://www.uptodate.com/contents/overview-of-atrial-flutter].
- [28]. JR.Hampton, The ECG made easy. 5th ed. London: Churchill Livingstone; 2001.
- [29]. PJ.Schwartz, MJ.Ackerman, AL.George, AMA.Wilde, Impact of genetics on the clinical management of channelopathies. J Am Coll Cardiol 2013; 62: 169– 80.
- [30]. Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press [http://www.medicinescomplete.com].
- [31]. Sudden Arrhythmic Death Syndrome. Drugs to avoid [https://www.sads.org.uk/drugs-to-avoid/].
- [32]. L.Dawn Adamson, N.Catherine, and Colleagues. Managing palpitations and arrhythmias during pregnancy. Heart 2007;93:1630-1636.
- [33]. Van Oppen AC, Stigter RH. Bruinse HW. Cardiac output in normal pregnancy: a critical review. Obstet Gynecol 1996; 87(2):310.
- [34]. Gerald G. Briggs, K. Roger Freeman, Sumner JY. Drugs in Pregnancy and Lactation. Lippincott Williams and Wilkins; 9th Revised edition: NY; 2011; 1224:1703.
- [35]. JA.Joglar, RL. Page Treatment of cardiac arrhythmias during pregnancy: safety considerations. Drug Saf. 1999; 20:85–94.