Zagazig University Medical Journal
www.zumj.journals.ekb.eg

Is Oral Anticoagulant with High Dose in Pregnant Women with Prosthetic Mechanical Valve Effective and Safe?

Mohammad El Tahlawi [I*], Nezar Elnahal [II], Amir Abdelsayed [II], Marwa Tharwat [III], Mohammad Alanwar [II]

[I] *Cardiology Department, Faculty of Medicine, Zagazig University, Egypt*
[II] *Cardiothoracic Surgery Department, Faculty of Medicine, Zagazig University, Egypt*
[III] *Anatomy&EmberyologyDepartment, Faculty of Medicine, Zagazig University, Egypt*

***Corresponding author:**
Mohammad El Tahlawi
Cardiology Department,
Faculty of Medicine,
Zagazig University,
Zagazig, Egypt
Email:
tahlawi_basha@yahoo.com

Submit Date: 03-02-2020
Revise Date: 12-03-2020
Accept Date: 17-03-2020

ABSTRACT

Background: The management of women with prothetic valves During pregnancy remains challenging. Anticoagulation in these subgroups has many controversies. We aim to evaluate the safe dose of oral anticoagulant in pregnant women with mechanical valve prosthesis in first trimester. **Methods:** Pregnant ladies with well functioning prothetic valves were enrolled. Patients were divided into 3 groups: Group A took oral anticoagulant < 5 mg warfarin with therapeutic INR. Group B took low molecular weight heparin (LMWH) twice daily and monitoring is done every week by antifactor Xa 4-6 hours post-injection to keep about 1 IU/ml. Group C took oral anticoagulant in dose > 5 mg warfarin to reach therapeutic INR. **Results:** There was significant difference between groups in vaginal bleeding and abortion, with more bleeding and abortion in group B using LMWH. There was a high rate of malfunction valve about 19.9% in group B, but no reported cases of malfunction valve in the other both groups using warfarin. **Conclusion**: Warfarin with dose > 5 mg in pregnant women with mechanical prosthetic valve is as safe for mother and baby as warfarin with dose < 5 mg. Both regimens are safer than LMWH.

Key Words: Oral anticoagulant, Warfarin, Pregnancy, Prothetic valve, Heparin, Teratogenic.

INTRODUCTION

The pregnancy considers a unique set of problems for any woman with prosthetic mecahncial valve [1].

There is an increase of incidence of thromboembolic events during pregnancy with prosthetic mechanical valves [2].

During pregnancy, there is an increase in haemodynamic load, stroke volume and heart rate. Also, there is an increase of cardiac output about 30% to 40% with decrease in total peripheral resistance leading to decrease in blood pressure [3-5].

The elevation of circulating procoagulant factors and maternal hormones leading to decrease in prothrombin time, activated partial thromboplastin time, thrombin time and INR [6,7].

Thromboembolism rates have been to be between 7% to 23% per patient per year in pregnant women with prosthetic mechanical valves [8].

The recent guidelines give class I recommendations to warfarin during the second and third trimester, because the risk of warfarin embryopathy is confined to weeks 6-12[9].

During the first trimester, wafarin at 5 mg/day or less gets class IIa rating making it

preferableto unfractionated or low-molecular-weight heparin [9].

Heparin is far less effective anticoagulant plus there is multiple study indicating risk of embryopathy is low-roughly 1% to 2% when mother is on warfarin at 5 mg/day or less [10].

Alternatives to warfarin are adjusted-dose unfractionated heparin, which must be given in continuous infusion with meticulous monitoring of activated PTT or twice-daily-low molecular-weight heparin with dose adjustment by weight and maintenance of target anti-factor Xa level of 1-1.2 IU/ml which must be done every week 4-6 hours postinjection [11].

The aim of this work was to evaluate the safe dose of oral anticoagulant in pregnant women with mechanical valve prosthesis in first trimester.

METHODS

The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

This retrospective study was performed on 90 pregnant women with mechanical valve prosthesis follow up in outpatient clinic.

Inclusion criteria:

We included all patients with prepregnancy echocardiography that shows well functioning valve, with no other valve lesion and good LV and RV function, no previous history of repeated abortion, Normal renal and hepatic functions & CBC, no previous history of malfunction valve,
and no previous history of bleeding disorder.

Exclusion criteria:

We excluded patients with other valve lesion, bad LV or RV function, history of repeated abortion or gynecological causes of abortion, renal or hepatic impairment, history of redo-operation due to malfunction of valve, history of bleeding disorders, patients needing warfarin more than 10 mg and patients with malfunction valve during the study.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the our institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Protocol of study

Informed consent was obtained from all individual participants included in the study. All patients received 5 mg warfarin as per guideline advice to reach target INR.

If the dose of 5 mg warfarin can not achieve target INR, patient was asked to take low molecular weight heparin (Clexan) twice daily with follow up factor Xa level (1-1.2 IU/ml) to reach therapeutic effective dose.

Some patients who were missing the follow up, increased their warfarin dose above 5mg by themselves to reach the instructed target INR.

All patients after first trimester received warfarin safely until labour, stopped 2 weeks before expected date for delivery and started heparin infusion in hospital until labour.

Patients were divided into 3 groups: ***Group A*** took oral anticoagulant < 5 mg warfarin with therapeutic INR. ***Group B*** took LMWH twice daily and monitoring is done every week by antifactorXa 4-6 hours post-injection to keep about 1 IU/ml. ***Group C*** took oral anticoagulant in dose > 5 mg warfarin to reach therapeutic INR.

Statistical analysis

Continuous variables were expressed as the mean ± SD and the categorical variables were expressed as a number(percentage). Continuous variables were checked for normality by using Shapiro-Wilk test. One way ANOVA test was used to compare more than two groups of normally distributed data. Percent of categorical variables were compared using Chi-square test. All tests were two sided. p-value< 0.05 was considered statistically significant. All data were analyzed using Statistical Package for Social Science for windows version 18.0 (SPSS Inc., Chicago, IL, USA), and Microsoft Office

Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA).

RESULTS

Each group involved 30 patients.

In the 3 groups, the age of pregnant women ranged from 20 to 35 years with no significant difference between groups.

No significant difference between groups regarding to types of valve and number of prosthetic mechanical valves (table 1).

There was significant difference between groups in vaginal bleeding and abortion, with more bleeding and abortion in **group B** using low molecular weight heparin (13.3%) , and much less in both groups A & C using warfarin dose less than 5 mg & more than 5 mg respectively (3.3%).

Regarding to preterm labour, still birth and congenital anomalies, there was no significant difference between all groups.

There was a high rate of malfunction valve about 19.9% in **group B** using low molecular weight heparin, but no reportedcases of malfunction valve in the other both groups who use warfarin either in low or high doses (table 2), (Figure 1).

Table 1. Basic characteristics of the studied groups:

Basic characteristics	Group A (N=30)		Group B (N=30)		Group C (N=30)		p-value
Age (years)	28.73 ± 3.50		27.20 ± 2.24		26.90 ± 3.45		0.056*
Type of valve							
MVR	18	(60%)	16	(53.3%)	19	(63.3%)	0.953§
AVR	3	(10%)	4	(13.3%)	3	(10%)	
DVR	9	(30%)	10	(33.3%)	8	(26.7%)	

N=Total number of patients in each group; MVR=Mitral valve replacement; AVR= Aortic valve replacement; DVR= Dual valve replacement. Quantitative data were expressed as the mean ± SD; Qualitative data were expressed as a number (percentage); * One way ANOVA test; § Chi-square test; p< 0.05 is significant.

Table 2. Outcome of the studied groups:

Outcome	Group A (N=30)		Group B (N=30)		Group C (N=30)		p-value§
Vaginal bleeding	1	(3.3%)	4	(13.3%)	1	(3.3%)	0.0200
Abortion	1	(3.3%)	4	(13.3%)	1	(3.3%)	0.0200
Preterm labor	1	(3.3%)	1	(3.3%)	1	(3.3%)	1.000
Still birth	0	(0%)	1	(3.3%)	0	(0%)	0.364
Congenital anomalies	0	(0%)	0	(0%)	0	(0%)	1.000
Malfunction valve	0	(0%)	6	(20%)	0	(0%)	0.002

N=Total number of patients in each group; Qualitative data were expressed as a number (percentage); § Chi-square test; p< 0.05 is significant.

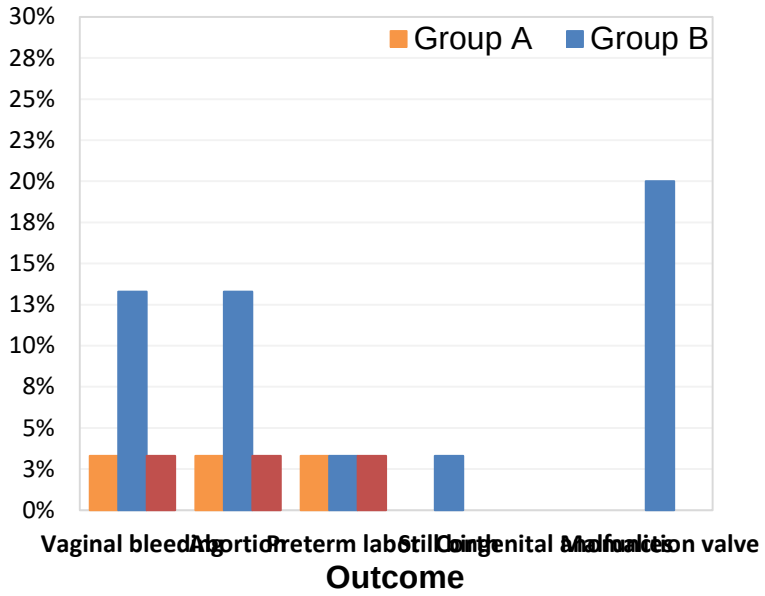

Figure 1. Bar chart shows Outcome of the studied groups

DISCUSSION

Malfunction prosthetic mechanical valves due to valve thrombosis are potentially life threatening complications. Due to hypercoagulable state of pregnancy, there is increase of the risk of valve thrombus of pregnant women with prosthetic mechanical valve [12].

On the other hand, inadequate anticoagulation, including the suspension of the oral anticoagulants aiming at fetal protection, carries a maternal risk of about 25% of metallic prosthesis thrombosis, particularly in the mitral valve [13].

There are controversies about the best anticoagulation during pregnancy in women with prothetic valve. Current recommendations, based on the literature, have been the replacement of warfarin sodium in the first trimester of pregnancy by low-molecular weight heparin (LMWH) until the 12th week of pregnancy. After this gestational age, warfarin is reintroduced until the 36th week of gestation and then replaced again by LMWH 24 hours before delivery [14].

Warfarin is the safest anticoagulant option for mother with rate of valve thrombosis about 2% [12] in comparing to high rate of valve thrombosis with unfractionated Heparin(UFH) (25% if used throughout pregnancy or 9.2% if used in first trimester) [15].

With use of low molecular weight heparin, the risk of thromboembolic complications has been about 12% [16].

In a recent meta-analysis comparing anticoagulation regimens for pregnant women with prosthetic heart valves, warfarin could provide better the best protection for the mother. while its teratogenic effects may be overestimated. In the same time, heparin does not provide better fetal outcomes as it is associated with severe adverse maternal outcomes, including mortality [17].

In our study, no cases hasembryopathy or any congenital anomalies in all groups.

There is only one case (3.3%) with preterm labour in all groups and one case (3.3%) with still birth in group B (LMWH) group.

CONCLUSION

According to our study, warfarin with dose > 5 mg in pregnant women with mechanical prosthetic valve is safe for mother and baby as warfarin with dose < 5 mg. Both doses are safer than LMWH.

Declaration of interest :
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
Funding information : None declared

REFERENCES

[1]. **Sillesen M, Hjortdal V, Vejlstrup N, Sørensen K.** Pregnancy with prosthetic heart

valves: 30 years' nationwide experience in Denmark. Eur J CardiothoracSurg. 2011; 40: 448.

[2]. **Hall JG, Pauli RM and Wilson KM.** Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med. 1980; 68: 122.

[3]. **Gilson GJ, Samaan S, Crawford MH, Qualls CR, Curet LB.** Changes in hemodynamics, ventricular remodeling, and ventricular contractility during normal pregnancy: A longitudinal study. Obstet Gynecol. 1997; 89: 957-962.

[4]. **Poppas A, Shroff SG, Korcarz CE, Hibbard JU, Berger DS, Lindheimer et al.** Serial assessment of the cardiovascular system in normal pregnancy: Role of arterial compliance and pulsatile arterial load. Circulation. 1997; 95: 2407-2415.

[5]. **Abbas AE, Lester SJ and Connolly H.** Pregnancy and the cardiovascular system. Int J Cardiol. 2005; 98: 179-189.

[6]. **Bremme KA.**Haemostatic changes in pregnancy. Best Pract Res ClinHaematol. 2003; 16: 153-168.

[7]. **Hui C, Lili M, Libin C, Rui Z, Fang G, Ling G, et al.** Changes in coagulation and hemodynamics during pregnancy: A prospective longitudinal study of 58 cases. Arch Gynecol Obstet. 2012; 285: 1231-1236.

[8]. Roudaut R, Serri K and Lafitte S. Thrombosis of prosthetic heart valves: Diagnosis and therapeutic considerations. Heart. 2007; 93: 137-42.

[9]. **Basude S, Hein C, Curtis SL, Clark A, Trinder J.** Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: What are the risks? A retrospective observational study. BJOG. 2012; 119: 1008-1013.

[10]. **Yinon Y, Siu SC, Warshafsky C, Maxwell C, McLeod A, Colman JM, et al..** Use of low molecular weight heparin in pregnant women with mechanical heart valves. Am J Cardiol. 2009; 104: 1259-1263.

[11]. **Quinn J, Von Klemperer K, Brooks R, Peebles D, Walker F, Cohen H.**Use of high intensity adjusted dose low molecular weightheparin in women with mechanical heart valves during pregnancy: A single-center experience. Haematologica. 2009; 94: 1608-1612.

[12]. **McLintock C, McCowan LM and North RA.** Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG. 2009; 116: 1585.

[13]. **Garcez JD, Rosa VE, Lopes AS, Accorsi TA, Fernandes JR, Pomerantzeff PM, et al**. Patient Management with Metallic Valve Prosthesis during Pregnancy and Postpartum Period. Arq Bras Cardiol. 2015; 105(4): 426-429.

[14]. **Tarasoutchi F, Montera MW, Grinberg M, Piñeiro DJ, Sánchez CR, Bacelar AC, et al.** Brazilian Guidelines for Valve Disease - SBC 2011 / I Guideline Inter-American Valve Disease - 2011 SIAC. Arq Bras Cardiol. 2011; 97(5 Suppl 1):1-67.

[15]. **Sadler L, McCowan L, White H, Stewart A, Bracken M, North R.** Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. BJOG. 2000; 107: 245.

[16]. **Oran B, Lee-Parritz A and Ansell J.** Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. Thromb Haemost. 2004; 92: 747.

[17]. **Wang J, Li K, Li H, Zhu W, Sun H, Lu C.** Comparison of Anticoagulation Regimens for Pregnant Women with Prosthetic Heart Valves: A Meta-analysis of Prospective Studies. Cardiovasc Ther. 2017; 35:e12292.

To cite this article: El-Tahlawi M, Alanwar M, Elnahal N, Abdelsayed A and Tharwat T. Is Oral Anticoagulant with High dose in Pregnant Women with Prosthetic Mechanical Valve Effective and Safe?Zumj May. 2020(26) No.3,450-454.DOI: 10.21608/zumj.2020.23331.1717