Original Article

IMPACT OF VARIOUS ANTICOAGULATION REGIMENS ON MATERNO-FOETAL OUTCOMES IN PREGNANT FEMALES WITH MODERN MECHANICAL PROSTHETIC MITRAL VALVE

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SA:Conducted the study and wrote the article. MS: Helped in review the article. WR: Re-arranged data and corrected article. SN: Tables and figures. SG and MI made corrections and did the proof reading.

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ABSTRACT

OBJECTIVE:Assessment of the pros and cons of anticoagulation in patients with mitral valve replacement with mechanical bileaflet valve is necessary when they become pregnant. We compared the incidence of adverse maternal and fetal outcomes with varioius anticoagulation regimens in this population to assess the risk of materno-foetal outcomes.

METHOD AND MATERIALS: This Prospective observational cohort study conducted at OPD of Punjab Institute of Cardiology Lahore, from January 2012 to December 2017.All female patients between 21-25 years of age who underwent Mitral valve surgery with Bileaflet prosthetic mechanical valve, using tablet warfarin to maintain their INR between 2.5 to 3.5, and have recently married were included in the study, and were followed up till the outcome of first pregnancy. All patients were followed up by their Obstetricians and Cardiologists & regularly visited Cardiac Surgery OutpatientsClinics. Authors have no role in placing patients on any of treatment regimens, the later being advised by their concerned Obstetrician and Cardiologist. Group A patients were advised to take UFH+Warfarin regimen. Group B patients were put on LMWH+Warfarin. Group C patients received tablet warfarin throughout pregnancy.

RSULTS: Mostly no difference of fetomaternal outcomes were detected among all three groups, however APGAR score and Fetal birth weight were significantly associated with Group A & B.

CONCLUSION:Warfarin alone therapy is as effective as other regimens, with even less maternal and fetal side effects.

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INTRODUCTION

In Pakistan, most common cause of Mitral valve disease is Rheumatic fever during childhood.[1] The patients usually present in late teens or early twenties to seek medical advice for their symptoms.[1] Those who were found treatable by surgical procedure, as per AHA and European Guidelines for valve management, got assessment for either repair or replacement with or without preservation of chordae tendineae.[2-4] The replacement of mitral valve is usually performed with Bileaflet mechanical valve.[3,4]

As mechanical heart valves are thrombogenic, these patients usually need anticoagulation with coumarin derivatives (e.g. warfarin) to prevent adverse outcomes like thrombosis, cerebrovascular events or even death.[3] The regimen is usually life long. When there is no contraindication for its use, warfarin is efficacious in reducing such life threatening events, thus making it a standard therapy.[4]

Surpisingly, despite hemodilution during pregnancy, decrease in the levels of Protein S, resistance to Protein C, alongwith impairment in fibrinolysis, there is an increase in thromboembolic events. This may lead to thromboembolism and prosthetic valve failure in pregnant females.[3] Additionally, these patients have an incidence of uncomplicated pregnancy and live birth in 58% of cases.[5] This is because warfarin crosses the placenta and is teratogenic. This results in high fetal loss and fetal abnormalities demanding an alternative like heparin (both fractioned, unfractionized heparin, and Low Molecular Weight, LMWH) for either the whole duration of pregnancy or only during the period of first 8 weeks (embryogenic period).[4,6] However, studies have shown risk of maternal thromboembolic complications with LMWH.[7,8] The most widely referenced systemic review by Chan et al6 was written long before the use of LMWH and studies on patients who underwent mitral valve replacement with ball in cage valve, which is not used since long, limiting the relevance of this review. These studies make ideal anticoagulation regimen a controversial issue.[4,9,10] This makes a large number of patients and their physicians reluctant to adopt to guidelines in Europe and United states, to use warfarin during pregnancy, however, ambiguousness exits about what to use instead and when to use it.

Assessment of the pros and cons of anticoagulation in patients with mitral valve replacement with mechanical bileaflet valve is necessary when they become pregnant. The goal of this study was to compare the incidence of adverse maternal and fetal outcomes with three anticoagulation regime used in our population of pregnant females with modern mitral mechanical heart valve.

MATERIALS & METHODS

This Prospective observational cohort study with non-probability consecutive sampling, was conducted at Outpatient Department of Punjab Institute of Cardiology Lahore, from January 2012 to December 2017.

Patients: All female patients between 21-25 years of age who underwent Mitral valve surgery with Bileaflet prosthetic mechanical valve, using tablet warfarin to maintain their INR between 2.5 to 3.5, and have recently married were included in the study, and were followed up till the outcome of first pregnancy. Patients married before mitral valve replacement, having prior pregnancy, with associated corrected congenital heart diseases, and comorbidities e.g. Diabetes, congenital blood dyscrasias, smoking, family history of abortions, using sub-therapeutic, unadjusted or unclear anticoagulation regimens, warfarin regimen demanding more than 5mg dose daily, if fixed doses of UFH were administered, were excluded from this study.

Intervention: Declaration of Helsinki was properly applied in study. All patients included in the study, were counselled about the issues related to become pregnant with outcomes. Considering non-interventional nature of the study, they all agreed to be part of the study. Ethical approval was taken from the Institute. A written informed consent was taken. Each patient was followed up for 3 years only from the date of their marriage.

Data Collection: All patients were followed up by their Obstetricians and Cardiologists & regularly visited Cardiac Surgery Outpatient Clinics. These patients were managed actively by Obstetricians with guidance from their Cardiologists. The role of Cardiac Surgeon was to collect the data as regards their management and the outcome of pregnancy. Authors have no role in placing patients on any of treatment regimens, the later being advised by their concerned Obstetrician and Cardiologist. The patients were divided into three group. Group A patients were advised to shift on iv unfractionized heparin 5000 IU (keeping their aPTT twice the control) for the first 2 months as per LMP dates, and then shifted back to Tablet Warfarin (dose adjusted according to required INR). After 8 months patients were again started on intravenous unfractionized Heparin 5000 IU (dose adjusted to keep APTT1.5

times the control) till they deliver, after which they were gradually shifted back to tablet warfarin (dose adjusted according to required INR). Group B patients were advised to shift on Low molecular weight Heparin (LMWH), enoxaparin sodium, initially 1 mg/kg twice daily and then adjusted for the first 2 months as per LMP date and then shifted back to Tablet Warfarin (dose adjusted according to required INR). After 8 months patients were again started on LMWH till they deliver, after which they were gradually shifted back to tablet warfarin (dose adjusted according to required INR). Group C patients were advised to continue with tablet warfarin throughout the pregnancy (dose adjusted according to required INR).

Outcome of Interest: A predesigned performa was used, which included **primary maternal outcomes** like maternal mortality (a death of pregnant female either during pregnancy or in the first 6 weeks postpartum), prosthetic valve failure (abnormal valve function leading to clinically meaningful outcome like heart failure, arrhythmias or reoperation) and thromboembolic events (valvular thrombi and extra valvularthromboemboli). In **secondary maternal outcomes** we placed major eclampsia, maternal bleeding (blood loss necessitating blood transfusion, readmission to hospital, interruption of anticoagulation therapy, drop in hemoglobulin by >20mg/dl, or surgery), placental rupture (separation of placenta before the fetus is delivered), maternal cardiac events (arrhythmias, heart failure and non-thrombotic valvular dysfunction), hypersensitivity to anticoagulant, and heparin induced thrombocytopenia. Also included were **primary foetal outcomes** like live births (proportion of pregnancies that culminated in live born infants) and embryopathy (nasal hypoplasia, stippled epiphyses, or both), foetopathy (ocular or central nervous system anomalies, excluding patent ductus arteriosus). As far as **secondary fetal outcomes** are concerned, the list included, fetal intracranial bleeding, small for gestational age (birth weight <10th percentile for gestation and sex), preterm birth (<37 weeks of gestation) and fetal loss (miscarriage at <20 weeks of gestation, still birth after 20 weeks of gestation, neonatal death after birth).

Clinical assessment with detailed history (emphasis on anticoagulation regimen, obstetric history, gestation age at delivery and mode of delivery, obstetric complications, perinatal complications, cardiac complications, medications used, results of INR/APTT during last three months, childs gender, birth weight and APGAR score) and proper examination of obstetric and cardiologists's documents were performed and noted on performa.

Statistical Analysis: IBM SPSS (Statistical Package for Social Sciences) for Windows version 21 used for data analysis. All qualitative variables were presented in the form of frequency tables, percentages, graphs and pie charts. Moreover, quantitative variables were presented in the form of mean±standard deviation and bar charts. In any groups Pearson chi-square test, Fischer Exact Test & regression analysis were thought to be considered. A p-value of ≤0.05 was taken as significant.

RESULTS:

A total of 117 patients were enrolled in the study. During the study period only 87 fulfilled the criteria of inclusion and exclusion. Thus the results

Table 1:Frequency of Feto-materal outcomes observed during the study time.

	Group A (n=20)	Group B (n=28)	Group C (n=39)
Age	22.5±0.688	21.96±1.036	23.38±1.600
Mode of Deliver			
• NVD	09	17	20
• D&C	07	07	10
• Caesarean Section	04	03	06
Maternal Mortality	00	03	05
Prosthetic Valve Failure	00	00	01
Thromboembolic Events	00	01	03
Eclampsia	00	00	03
Postpartum Hemorrhage	01	04	01
Placental Rupture	00	02	03
Maternal Cardiac Events			
• Arrhythmias	02	01	05
• Heart Failure	00	01	01
• Non-Thromboembolic event	00	00	00
Hypersensitivity of Anticoagulant	02	02	00
Heparin Induced Thrombocytopenia	00	00	02
Live births	18	21	34
Embryopathy	02	06	02
Fetopathy	00	01	04
Fetal Intracranial Bleeding	00	00	01
Small for Gestational Age			
• Neonatal Death	08	07	07
• Miscarriage	00	02	01
• Still birth	01	00	00
• None	11	19	31
Fetal Loss	00	04	02
Preterm Birth	03	05	03
Birth weight			
• >5.5lb	08	03	17
• 4.5-5.5lb	03	13	11
• <4.5lb	09	12	11
APGAR Score			
• 4	00	03	01
• 5	01	04	02
• 6	00	08	03
• 7	10	08	13
• 8	09	02	18
• 9	00	03	02

are based on those 87 patients.

The Table 1 shows the impact of anticoagulant regimens with fetomaternal outcome.

In Group A, non-significant relation was detected again stprosthetic valve failure (p=0.468), Thromboemolic events (p=0.143), Postpartum hemorrhage (p=0.693), Placental rupture (p=0.100), Maternal Cardiac Events (p=0.586), Hypersensitivity to Anticoagulant (p=0.227), HIT (p=0.3.3), fetal intracranial bleed (p=0.468), Embryopathy (p=0.809), Fetopathy (p=0.10), Preterm Birth (p=0.722), SGA (p=0.060), Birthweight (p=0.179), Fetal loss (p=0.071). However, there was significant relation found with APGAR Score (p=0.022).

In Group B, no relation was observed with maternal mortality (p=0.737), prosthetic valve failure (p=0.376), Thromboemolic events (p=0.748), Postpartum hemorrhage (p=0.072), Placental rupture (p=0.705), Maternal Cardiac Events (p=0.361), Hypersensitivity to Anticoagulant (p=0.450), HIT (p=0.209), fetal intracranial bleed (p=0.376), Embryopathy (p=0.054), Fetopathy (p=0.532), Preterm Birth (p=0.325), SGA (p=0.512), Fetal loss (p=0.072). Surprisingly, significant relation was detected with APGAR Score (p=0.000) and birthweight (p=0.005).

When results in Group C are analyzed, there was insignificant relation of warfarin therapy with maternal mortality (p=0.292), prosthetic valve failure (p=0.203), Thromboemolic events (p=0.209), Postpartum hemorrhage (p=0.130), Placental rupture (p=0.483), Maternal Cardiac Events (p=0.563), HIT (p=0.071), fetal intracranial bleed (p=0.203), Embryopathy (p=0.081), Fetopathy (p=0.097), Preterm Birth (p=0.201), APGAR Score (p=0.259), SGA (p=0.285), Birth weight (p=0.107), Fetal loss (p=0.553). Nevertheless there was significant relation found with Hypersensitivity to Anticoagulant (p=0.027).

DISCUSSION:

Addressing the relation of three usual treatment modalities with maternal and fetal outcomes of pregnancy is difficult and debatable topic. A meta-analysis considering studies of Chan,[6] James,[7] Oran,[8] & Zachary[12] et al, found when 800 patients were treated with modern anticoagulation regimens, warfarin and associated drugs are linked with lowest risk of adverse maternal events. Furthermore, Vitale,[13] and Zachary[12] et al have also described that risk of maternal outcomes are lower for warfarin and associated drugs when compared to dose adjusted LMWH given throughout pregnancy. However, James et al[7] reported a lower incidence of maternal thromboembolic complications.

It was suggested by Iturbe et al,[14] that warfarin and like drugs are associated with high incidence of spontaneous abortion. However, the incidence of fetal death in their study was quite low. Wang et al,[15] however, are of the opinion that heparin does not provide better fetal outcomes and the tetratogenic effects of warfarin may be overestimated. We highly agree with their description, as our own study detected a significant relation of Group B treatment with APGAR and Birthweight.

Like Nishimura et al,[4] we support the notion of AHA guidelines, to use of low dose warfarin in pregnant females who maintain their INR within the therapeutic range, however the dose may not exceed 5mg per day.

CONCLUSION:

There is no hazard in continuous use of Warfarin and like drugs throughout pregnancy, with similar maternal and fetal outcomes, when compared with UFH or LMWH based regimens in our population of study.

LIMITATIONS:

Our data is not randomized, therefore direct comparison among regimens should be considered as exploratory and be interpreted with caution, when there is possibility of confounding variables.

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