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Original Research Article

Comparison between two different regimens of anticoagulants for pregnant women with prosthetic heart valves

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ABSTRACT

Background: The current study aims to assess the maternal and fetal outcomes of pregnant females with prosthetic heart valves receiving oral anticoagulants only versus the sequential regimen of heparin and OA throughout pregnancy.

Methods: An observational was carried out at Assiut Women's Health Hospital, Egypt between February and December 2016. All pregnant women with prosthetic heart valves attending the emergency department during the study period were enrolled in the study. All included patients were classified into two groups; women who receive low molecular weight heparin (LMWH) during the first trimester then shift to warfarin till 36 weeks of gestation then continue on LMWH till delivery (Group I) and those who continue the all period of pregnancy on warfarin (Group II). The primary outcome of the study was the difference in the rate of maternal cardiac complications during labor between both groups.

Results: The study included 72 patients have prosthetic valve replacement and on anticoagulants. Twenty-one were on oral anticoagulant; warfarin (Group II) and 51 pregnant women were on sequential regimen. Both groups were comparable in their basic and clinical data on admission. No difference between both groups in the mode of delivery (p=0.52), postpartum hemorrhage (0.09), sub rectal hematomas (p=0.08), the need for postpartum admission to ICU (p=0.93) and the duration of hospital stay (p=0.47). Additionally, no statistical significant difference between both groups as regard the mean birth weight (p=0.97), Apgar score (p=0.62), fetal sex (p=0.92) and congenital anomalies (p=0.08).

Conclusions: The use of sequential LMWH and oral anticoagulants appears to be a safe option for those women although there is no difference in maternal and fetal outcomes with the use of continuous oral anticoagulants throughout the pregnancy.

Keywords: Anticoagulants, Heparin, Mitral replacement, Rheumatic heart disease, Warfarin

INTRODUCTION

The number of females with mechanical valves who become pregnant are rising, especially in developing countries where the rate of rheumatic heart disease complicated by valvular lesions is still high. Many of those patients undergo valve replacement surgeries at a young age; later they get pregnant.

All patients with mechanical heart valves should be on long-term anticoagulation to prevent the catastrophic complications of valve thrombosis which can lead to systemic embolism. This is especially right during pregnancy when prothrombotic changes occur throughout pregnancy, labour and delivery which increases the risk of mechanical heart valve thrombosis.[1,2]

However, there is no perfect anticoagulant for pregnant females, as the effect of anticoagulant on the fetus must be well-thought-out as well as the safety of the mother.[3-5]

Oral anticoagulants (OA) have the best protection against thrombosis, but their use is associated with a significant risk of fetal deformities and pregnancy loss. Replacing OA with heparin decreases the risk of fetal damage, but increases the risk of valve thrombosis, even when given in adjusted doses.[6,7]

The aim of the current study was to assess the maternal and fetal outcomes of pregnant females with prosthetic heart valves receiving oral anticoagulants only versus the sequential regimen of heparin and OA during the course of pregnancy.

METHODS

The current study was an observational study conducted at Assiut Women's Health Hospital, Egypt between February 2016 and December 2016. The Assiut Medical School Ethical Review Board approved the study. Written consent to participate had been obtained from all study participants.

Study population

All pregnant women with prosthetic heart valves attending the emergency department of the aforementioned hospital during the study period were invited to participate in the study.

The inclusion criteria were; age 15-40 years, pregnant at any trimester and on anticoagulant therapy. We excluded women with chronic medical illnesses as diabetes and hypertension, women with congenital or ischemic heart diseases and those who declined participation in the study.

Intervention

One of the study investigators collected the basic data including; age, parity, previous miscarriages and body mass index (BMI). Then, a detailed history was taken regarding the antenatal visits, anticoagulation regimen, use of long acting penicillin, obstetric history, previous heart failure and history of intensive care unit (ICU) admission before.

Thorough clinical examination was done to find out any signs of failure and stage of pregnancy. Cases were graded as per NYHA classification of grade of heart disease. All included patients were classified into two groups; women who receive low molecular weight heparin (LMWH) during the first trimester then shift to warfarin till 36 weeks of gestation then continue on LMWH till delivery (Group I) and those who continue the all period of pregnancy on warfarin (Group II).

Follow-up

All women were followed up during the course of delivery according to the hospital protocol. Any cardiac or obstetric complications occurred during labor or postpartum were recorded. Data at delivery was obtained including; gestational age at delivery and mode of delivery. Additionally, fetal weight, gender, Apgar score at delivery, presence of congenital malformations and rate of stillbirths were recorded.

The need for postpartum admission to ICU, duration of hospital stay and cases of maternal mortality were also recorded.

Study outcomes

The primary outcome of the study was the difference in the rate of maternal cardiac complications during labor between both groups. The secondary outcomes were the difference in the, mode of delivery, fetal birth weight and the rate of congenital malformations.

Statistical analysis

The collected data was coded; tabulated and analyzed using the statistical package for social science programs (SPSS) Chicago, IL, USA, version 22. Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed as frequency and percentage. Comparison between groups was done using Mann-Whitney for quantitative variables and Fisher's exact test for qualitative variables. Level of significance "P" value was evaluated, where P value <0.05 was considered statistically significant.

RESULTS

During the study period, 72 patients have prosthetic valve replacement and on anticoagulant were included in the study. Twenty-one pregnant women were on oral anticoagulant; warfarin (Group II) as they use it pre-conception till delivery. Dose of warfarin for all patients was between 2.5 and 4.5g /day except four patients, it was > 5g /day and INR at time of delivery range between 2.5 and 3.5 for all patients. On the other hand, 51 pregnant women were on LMWH during the first trimester and shifted to warfarin till 36 weeks' gestation and then continue on LMWH till delivery (Group I). They were receiving therapeutic dose of LMWH. Of the 72 patients included at the study, there were 62 patients were undergone mitral replacement (86.1%), 4 patients were undergone aortic replacement (5.5%), 4 patients were undergone combined aortic and mitral replacement (5.5%) and finally two patients had combined tricuspid and mitral replacement (2.8%).

Table 1 show that both groups were comparable in their basic and clinical data on admission.

Table 2 summarizes the maternal outcomes of prosthetic heart valves patients during labor. No difference between both groups in the mode of delivery (p=0.52), postpartum haemorrhage (0.09), sub rectal hematomas (p=0.08), the need for postpartum admission to ICU (p=0.93) and the duration of hospital stay (p=0.47).

Table 3 demonstrates no statistical significant difference between both groups as regard the mean birth weight (p=0.97), Apgar score (p=0.62), fetal sex (p=0.92) and congenital anomalies (p=0.08). No cases of stillbirths in both groups.

Table 1: The basic and clinical data of the study participants.

Variables	Prosthetic valves (n=72)				p-value
	Group I		Group II		
Age (years) #	30.4±5.4		31.8±4.9		0.06
Parity #	1.94±1.5		2.3±1.9		0.36
BMI #	22.85±2.6		22.98±2.2		0.67
	N=51	%	N=21	%	
Past ICU admission	3	5.9	2	9.5	0.18
Previous heart failure	5	9.8	2	9.5	0.92
NYHA classification					
Grade 1	22	43.1	7	33.3	0.31
Grade 2	16	31.4	11	52.4	
Grade 3	10	19.6	3	14.3	
Grade 4	3	5.9	0	0	

Group I: Sequential LMWH and warfarin, Group II: warfarin only. BMI; body mass index, ICU; intensive care unit, (#) Data are presented as mean ± standard deviation.

Table 2: The maternal outcomes during labor.

Outcomes	Prosthetic valves (n=72)				p-value
	Group I		Group II		
	n=51	%	n=21	%	
Mode of delivery *					
Vaginally	19	37.3	8	38.1	0.52
CS	25	49.0	10	47.6	0.09
Postpartum hemorrhage	16	31.3	10	47.6	0.93
Postpartum admission to ICU	18	35.3	7	33.3	0.47
Duration of postpartum hospital stay (days) #	5.12±4.6		4.33±4.67		0.47
Subrectal hematomas	0	0	2	9.5	0.08
Maternal deaths	2	3.9	0	0	0.53

Group I: Sequential LMWH and warfarin, Group II: warfarin only. (*) There are 7 cases in group I and 3 cases in group II had second trimester miscarriage. CS; cesarean section, ICU; intensive care unit, (#) Data are presented as mean ± standard deviation.

Table 3: The neonatal outcomes of the study participants.

Outcomes	Prosthetic valves (n=72)				p-value
	Group I		Group II		
	n=51	%	n=21	%	
Birth weight (gram)#	2890.9±654.4		2883.3±613.8		0.97
Apgar score#	8.36±1.39		8.06±1.7		0.62
Neonatal gender*					
Male	22	50	10	55.6	0.92
Female	22	50	8	44.4	
Stillbirths	0	0	0	0	------
Congenital malformations	0	0	2	9.5	0.082

Group I: Sequential LMWH and warfarin, Group II: warfarin only. (*) There are 7 cases in group I and 3 cases in group II had second trimester miscarriage. (#) Data are presented as mean±standard deviation.

DISCUSSION

Pregnancy induces changes in the haemostatic mechanism predisposing these females to hypercoagulable state which can lead to thromboembolic complications. This change includes Increase in the concentration of circulating clotting factors, faster platelet turnover and decrease in the fibrinolytic activity. These changes sideways with the presence of mechanical valves are associated with increased risks of thromboembolic risks.[7]

Pregnancy in females with mechanical heart valves still a challenge to the obstetrician and the cardiologist. The main worry concerning the treatment during pregnancy is the teratogenic effect of the different anticoagulants on the fetus and the risk of thromboembolic complications for the mother.

LMWH has better bio-availability and less hemorrhagic complications than oral anticoagulant. Additionally, it does not cross the placenta, so it doesn't have teratogenic effect on the fetus. The American College of Obstetricians and Gynaecologists (ACOG) stays to warn against the usage of LMWHs in these patients because of documented cases of associated valve thrombosis and it also necessitates anti-Xa checking in pregnancy. In our study, there were no cases of thromboembolic complications in those receives oral anticoagulant but there are 2 cases of valve thrombi in those receiving LMWH.[8,9]

On the other side; oral anticoagulants may cause embryopathy, and central nervous system abnormalities. In order to prevent possible side effects of oral anticoagulant on the fetus, heparin is recommended to replace the oral anticoagulant before the most vulnerable period of embryogenesis. Oral anticoagulants have the greatest risk of embryopathy when given between the 6th and the 12th week of pregnancy which is found to be associated with abortions and late fetal loss.[6,10]

This presents pregnant females with the difficult choice: to take a drug such as warfarin that is the safest for her but may badly affect her fetus or to take heparin that may increase her risk of thrombosis of her mechanical valve and may lead to systemic thrombi but will not directly affect her fetus. Undoubtedly, the risk of death for pregnant female who develops a thrombosis or requires redo cardiac surgery for a thrombosed valve must be taken in concern into the comparison when considering the advantages and side effects of each treatment option.

In present study, there is no significant difference in fetal outcomes regards the abortion, still birth, Apgar score and congenital malformation between the 2 groups. The value of replacing oral anticoagulants with heparin in the first trimester to decrease the spontaneous abortion rate is not substantiated in newer studies.[10]

In present study, there are only 2 cases of congenital anomalies of 21 patients received oral anticoagulant (9.5%), one with Dandy–Walker malformation and the other with nasal hypoplasia and stippled epiphyses. The first detected by antenatal ultrasound at 20 weeks and the later detected after delivery.

The new studies detected there is association between the dose of oral anticoagulant and embryopathy as a dose of more than 5 mg is associated with adverse effects.[11] In our study all patient received dose <5 g /day except 4 patients (2 received 7.5g/day, one received 9 g/day and one 12g/day), 2 of them (7.5g/day, 9g/day) got baby with congenital anomalies and one (12g/day) complicated by missed abortion at 19 wks. However, statistically in our study there is no significant difference regards abortion and congenital anomalies between the 2 groups.

Enhanced fetal outcomes in pregnant women received heparin as anticoagulant has long been documented and LMWH is the anticoagulant drug of choice in pregnant females who need thromboprophylaxis or acute treatment of venous thromboembolism. Yet the effectiveness of heparin in prevention of thromboembolic complications in females with mechanical valve is argued. Available studies of females who receive heparin throughout pregnancy in place of oral anticoagulant detected no congenital fetal anomalies but the rate of thromboembolic complications (33%) is unsatisfactorily high. Substitution of heparin for oral anticoagulant in the first trimester only is effective in stopping warfarin embryopathy, but high rates of late fetal loss and stillbirth rates remain with maternal thromboembolic complications in 9.5% of pregnancies.[12-16]

In 2002, Food and Drug Administration instructed a threatening in the package insert of enoxaparin, which specified that the product is not recommended for anti-thrombotic prophylaxis in patients with mechanical valves; as there are cases of mechanical valve thrombosis, maternal and fetal deaths were reported with the use of this drug; and that in pregnant women who received this drug, both teratogenic and non-teratogenic effects have been reported. Even so, the data on the use of enoxaparin in this subgroup of patients is mixed with literature available to both support and contraindicate its use.[17-20]

In present study, there are 2 patients received LMWH complicated by thromboembolism; one of them at 11 weeks of gestation and get treatment and pregnancy continue till full term on unfractionated heparin and the other at 5th day post-partum which ended by mother death. Due to financial issue, there was no follow up to patients received LMWH at our study by anti-Xa levels.

The need to decrease time off anticoagulation in these females at high risk of thromboembolism necessitates early use of anticoagulation postpartum and this may add to the high risk of primary and secondary postpartum

haemorrhage (PPH). Of specific worry are the high rates of secondary haemorrhage including wound haemorrhage following CS, but also vulval and perineal haemorrhage in women who have had normal vaginal delivery. In the Auckland cohort, main secondary haemorrhage was reported in 19% of women and primary PPH in 13%.[21]

In our study PPH occurred in 16 of 51 (31.37%) patients received LMWH and in 10 of 21(47.62%) patients received oral anticoagulants. Sub rectal hematoma formed only in 2 patients of the oral anticoagulant group after CS and didn't need evacuation; just follow up of the size of it.

In conclusion, anticoagulants use in pregnant women with prosthetic heart valves is essential for decreasing both maternal and fetal complications. The use of sequential LMWH and oral anticoagulants appears to be a safe option for those women although there is no difference in maternal and fetal outcomes with the use of continuous oral anticoagulants throughout the pregnancy.

CONCLUSION

Doppler sonography is an indispensable tool in evaluating pregnancies complicated with uteroplacental insufficiency. This study showed that of all the fetal Doppler parameters, umbilical artery-S/D ratio and umbilical artery-RI>2SD are significant predictors of adverse perinatal outcome like perinatal deaths and immediate resuscitation. Umbilical artery-PI >2SD was predictive of acute fetal distress in labour but on multivariate analysis failed to find any association. None of the Doppler parameters helped to predict neonatal nursery admission. Thus, Doppler parameters can help the obstetrician and neonatologist to plan delivery and minimize adverse perinatal outcomes.

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