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Original Article / Özgün Makale

Anticoagulation therapy in pregnant women with mechanical heart valve

Mekanik kalp kapağı olan gebe kadınlarda antikoagülasyon tedavisi

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ABSTRACT

Background: This study aims to investigate the effects of various anticoagulant regimens on prosthetic valve-related complications and pregnancy outcomes including feto-maternal mortality and morbidity, and to identify the most optimal anticoagulation therapy regimen.

Methods: Anticoagulant therapy regimens for pregnant women who underwent mechanical heart valve replacement between January 1990 and December 2015 was analyzed retrospectively. Seventy-two pregnancies among 57 patients after mechanical heart valve replacement were reviewed, and four different regimens were identified and evaluated during different trimesters of pregnancy.

Results: Forty of 72 pregnancies resulted in healthy newborns; 35 (48.6%) healthy neonates, four (5.6%) premature births, and one (1.4%) low birth weight. Eighteen (25%) therapeutic and 12 (16.7%) spontaneous abortions, as well as two (2.8%) stillbirths occurred. Seven valve thromboses developed during pregnancy or the postpartum period. Bleeding occurred in six patients (10.5%) and peripheral embolism also occurred in six patients (10.5%). No maternal mortalities were recorded.

Conclusion: Although there is no consensus on the most optimal anticoagulant regimen during pregnancy, substituting warfarin with dose-adjusted unfractionated heparin or low-molecular-weight heparin seems suitable to prevent teratogenicity and a high abortion rate in the first trimester. Low-molecular-weight heparin is practical to use and can be monitored reliably, resulting in successful pregnancy outcomes. However, warfarin throughout pregnancy ≤5 mg per day may be an alternative choice, if the risk of embryopathy is accepted by the pregnant woman.

Keywords: Anticoagulation; mechanical heart valve; pregnancy.

ÖZ

Amaç: Bu çalışmada, farklı antikolagülan rejimlerinin protez kapak ile ilişkili komplikasyonlar ve feto-maternal mortalite ve morbidite üzerindeki etkileri araştırıldı ve en ideal antikolagülan tedavi rejimi belirlendi.

Çalışma planı: Ocak 1990 - Aralık 2015 tarihleri arasında mekanik kalp kapak replasmanı yapılan gebe kadınlarda antikoagülan tedavi rejimleri, retrospektif olarak incelendi. Mekanik kalp kapak replasmanı sonrası 57 hastada 72 gebelik gözden geçirildi ve dört farklı rejim belirlendi ve gebeliğin farklı trimesterlerinde değerlendirildi.

Bulgular: Yetmiş iki gebeliğin, 40'ı sağlıklı yeni doğanla, 35'i (%48.6) sağlıklı yenidoğan, dördü (%5.6) prematüre doğum ve biri (%1.4) düşük doğum ağırlığı ile sonuçlandı. On sekiz (%25) terapötik ve 12 (%16.7) spontan düşüğün yanı sıra, iki (%2.8) ölü doğum izlendi. Gebelik süresince veya post-partum dönemde, yedi gebede kapak trombozu gelişti. Altı hastada (%10.5) kanama ve yine altı (%10.5) hastada periferik emboli meydana geldi. Maternal mortalite görülmedi.

Sonuç: Gebelik sırasında en ideal antikoagülasyon rejimine ilişkin tam bir fikir birliği olmamasına rağmen, birinci trimesterde varfarinin teratojenisite ve artmış düşük riskini önlemek için doz ayarlamalı fraksiyone olmayan heparin veya düşük molekül ağırlıklı heparin ile değiştirilmesi uygundur. Düşük molekül ağırlıklı heparinin uygulaması kolaydır ve güvenilir bir şekilde izlenebilir ve başarılı gebelik sonuçlarına da vesile olabilir. Ancak, gebeliğin tüm trimesterleri süresince, günde ≤5 mg varfarini geçmemek kaydıyla kullanılacak varfarin, embriyopati riskinin gebe tarafından kabul edildiği durumlarda, alternatif bir seçenek olabilir.

Anahtar sözcükler: Antikoagülasyon; mekanik kalp kapağı; gebelik.

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Prohibiting pregnancy in a woman of childbearing age with a mechanical heart valve prosthesis is not always acceptable. Due to the lack of randomized-controlled studies on this subject, a consensus has not been reached on the most optimal anticoagulant (AC) regimen, and only anecdotal and contradictory reports are available.[1,2]

The AC therapy chosen for use during pregnancy can place the fetus and mother at risk, and the morbidity and mortality risks are high for both. In addition to the risk of fatal maternal thromboembolic complications, fetal anomalies can occur. Hence, managing a pregnant woman with a prosthetic valve is very complicated.[3] Unfractionated heparin (UFH) is related to increased maternal bleeding, but avoids fetal anomalies.[4] Low-molecular weight heparin (LMWH) appears to be safer; however, little evidence is available on the use of LMWH for long-term anticoagulation in pregnant women with mechanical heart valves.[5] Although warfarin is the most effective AC, it is contraindicated in the first trimester of pregnancy due to its teratogenic effects.[6]

Many risk factors have been reported for prosthetic valve thrombosis, such as the type of the prosthetic valve implanted, size and position of the valve, presence of atrial fibrillation, left atrial diameter, adequacy of the AC therapy, medical history of stroke, hypercoagulability, advanced age, low ejection fraction, and age at mechanical valve implantation.[7]

In this study, we tried to identify the optimal AC therapy for pregnant women with mechanical heart valves and the feto-maternal complications resulting from AC therapy. Finally, based on our findings, we outlined certain recommendations that offer the most optimal feto-maternal outcome.

PATIENTS AND METHODS

The study was conducted by the principles of the Helsinki Declaration and approved by the local Institutional Review Board. A written informed consent was obtained from each patient.

Anticoagulant therapy for pregnant women who underwent mechanical heart valve replacement in our hospital between January 1990 and December 2015 was analyzed retrospectively. The distribution of various valve replacements is listed in Table 1.

A total of 57 patients, with a total of 72 pregnancies, were followed. The patients were referred to our hospital within the first 1 to 6 weeks of gestation. On presentation, after having explained the feto-maternal risks of pregnancy and the risks and benefits of AC therapy, the patients were initiated on the desired AC regimen and a plan was made for the remainder of the pregnancy. According to this, four main groups each with different regimens were identified. Group 1 involved 25 pregnancies, group 2 involved 31 pregnancies, and group 4 involved eight pregnancies. Another group (group 3) involved eight pregnancies in pregnant women who rejected using any type of AC, despite the aforementioned risks.

In group 1, warfarin treatment was discontinued and replaced with LMWH (22 pregnancies) or UFH (three pregnancies) during 6 to 12 weeks of pregnancy. During the second trimester, OAC was started and continued until 36 weeks of gestation for all 25 patients. Finally, the treatment regimen was changed to LMWH (22 pregnancies) or UFH (three pregnancies) during 36 to 38 weeks of pregnancy. The patients in group 2 were on warfarin and acetyl salicylic acid (ASA) simultaneously throughout their pregnancies. This group included 31 pregnancies. Group 3 involved patients with no AC and group 4 included patients who were on LMWH treatment throughout their pregnancies.

Therapeutic abortion was conducted using dilatation and curettage after adequate counselling and an informed consent was obtained. These patients either had children or the pregnancy was undesired.

Elective caesarean section (C/S) was the delivery choice; however; normal spontaneous vaginal delivery (NSVD) was also performed upon request of the patient and obstetrician. The lowest warfarin dose required to reach the target International Normalized Ratio (INR) value (2.5-3.5)[8] was administered to the patients. The four different AC regimes (groups) applied during the different trimesters of pregnancy are shown in Table 2.

Table 1. Distribution of valve replacements

Type of valve replacement	Number of patients (n=57)	Number of pregnancies (n=72)
Aortic valve replacement	2	2
Mitral valve replacement	52	66
Double valve replacement	2	2
Tricuspid valve replacement	1	2

Table 2. Anticoagulation regimens of patients

	1-6 weeks (pregnancy diagnosed)	6-12 weeks	12-36 weeks	36-38 weeks	Number of pregnancies (n)
Group 1	OAC	LMWH	OAC	LMWH	25
Group 2	OAC+ASA	OAC+ASA	OAC+ASA	UFH	31
Group 3	No AC	No AC	No AC	No AC	8
Group 4	LMWH	LMWH	LMWH	LMWH	8

OAC: Oral anticoagulation (warfarin); LMWH: Low-molecular weight heparin; ASA: Acetylsalicylic acid; UFH: Unfractionated heparin; No AC: No anticoagulation.

Anti-factor Xa levels were monitored once monthly, or not monitored, during administration of LMWH. The activated partial thromboplastin time value for UFH was adjusted to at least twice that of the control. Cardiac rhythm, history of embolization, and the pre-pregnancy AC dose were considered when adjusting the AC dose.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). The data were expressed in mean ± standard deviation (SD) for quantitative variables and in percentage for categorical variables. The groups were compared using the chi-square test (or Fisher's exact test, if required) for categorical variables. A p value of ≤0.05 was considered statistically significant.

RESULTS

In this study, 72 pregnancies among 57 patients were evaluated. There were 40 (55.6%) healthy newborns, 35 (48.6%) healthy neonates, four (5.6%) premature births, and one (1.4%) low-birth-weight newborn. Eighteen (25%) therapeutic and 12 (16.7%) spontaneous abortions, as well as two (2.8%) stillbirths, were observed. The pregnancy outcomes are shown in Table 3.

A total of 12% (3 in 25 pregnancies) spontaneous abortion were observed in group 1 (first trimester heparin or LMWH and then warfarin). In group 2 (warfarin + ASA throughout pregnancy), there was a 22.6% (seven in 31 pregnancies) spontaneous abortion rate. Spontaneous abortion was not significantly different between the first trimester heparin or LMWH and then warfarin group (group 1) and warfarin + ASA throughout pregnancy group (group 2) (p=0.485). However, when we compared spontaneous and therapeutic abortions together, the rates were 16% (4 pregnancies) and 77.4% (24 pregnancies) in group 1 and 2, respectively (p<0.001) (Table 4). In two cases, the mode of delivery was NSVD, whereas C/S was performed in the remaining cases upon patient request. No maternal mortalities were recorded.

Table 3. Outcomes of pregnancy

	n
Healthy neonates	35
Premature delivery	4
Low-birth-weight	1
Therapeutic abortion	18
Abortions (all during the first trimester)	12
Stillbirth	2*

* One occurring at 29 weeks gestation and one occurring at 34 weeks gestation.

Three patients developed valve thrombosis in the LMWH + OAC group (group 1); two of these had stuck valves at the beginning of the second trimester when LMWH was replaced with OAC, and one had a stuck valve during week 20 of pregnancy due to interrupted OAC therapy. The first two patients had their mitral valves replaced successfully and gave birth to healthy full-term babies via elective C/S, whereas the patient with a tricuspid valve replacement (TVR) Björk-Shiley mechanical valve (Shiley Inc, Irvine, CA, USA) presented with a valve gradient during week 20 of her sec pregnancy for which thrombolytic treatment was administered. This resulted in recession of the gradient and she was referred to an obstetrician to terminate the pregnancy due to possible fetal developmental anomalies and maternal risk. In these patients, OAC was commenced at the same dose as at the beginning of the pregnancy. Concomitant treatment with LMWH was given, until the desired INR value was reached. These patients underwent a new valve replacement under normothermic cardiopulmonary bypass with the high flow/high pressure perfusion technique.[9]

A left atrial thrombus occurred during replacement of UFH with OAC in group 1 resolved spontaneously without any further change in treatment.

Four of the seven patients who stopped their OAC therapy without consulting a doctor (group 3) underwent a repeat mitral valve replacement due to a stuck valve during the first 2 months postpartum. No mortalities were observed. Five healthy babies were born in this group.

Table 4. Abortion rates

	Group 1 LMWH + OAC		Group 2 OAC + ASA		
	n	%	n	%	*p*
Spontaneous abortion	3	12	7	22.6	0.485
Therapeutic abortions	1	4	17	54.8	<0.001
Total abortion	4	16	24	77.4	<0.001

LMWH: Low-molecular weight heparin; OAC: Oral anticoagulation (warfarin); ASA: Acetylsalicylic acid.

Table 5. Feto-maternal complications and pregnancy outcomes

	Pregnancy (n)	Bleeding	PE	VT	PVT	PD&LBW	HB	TA	SA	SB
Group 1										
LMWH + OAC	25	1		3			21	1	3	
Group 2										
OAC + ASA	33	5	5			3	4	17	7	
Group 3										
No AC	8		1		4		5		1	2
Group 4										
LMWH	8					2	5		1	

PE: Peripheral embolism; VT: Valve thrombosis; PVT: Postpartum valve thrombosis; PD: Premature delivery; LBW: Low-birth-weight; HB: Healthy baby; TA: Therapeutic abortion; SA: Spontaneous abortion; SB: Stillbirth; OAC: Oral anticoagulation (warfarin); ASA: Acetylsalicylic acid; No AC: No anticoagulation; LMWH: Low-molecular weight heparin.

Bleeding occurred in five patients in the OAC + ASA group (group 2) due to warfarin overdose and in one patient due to concomitant use of LMWH and warfarin in the LMWH + OAC (group 1). Among 72 pregnancies, six patients had a bleeding event, six had peripheral embolism, and seven had a valve thrombosis (three during pregnancy and four postpartum) as listed in Table 5.

Of 57 patients, 45 (79%) had atrial fibrillation, and 12 (21%) had normal sinus rhythm.

DISCUSSION

The most suitable heart valve choice and appropriate AC regimen for pregnant women are controversial; however, the inappropriateness of preventing a pregnancy in a woman who desires to have a child is clear.

Warfarin is contraindicated during the first trimester of pregnancy to avoid teratogenic effects. Although warfarin is the most effective AC, LMWH or UFH has replaced warfarin in most studies, as these agents do not cross the placenta and have no teratogenic effects.[6] Heparin, due to its short duration of action, it has some disadvantages including thrombocytopenia, osteoporosis, retroplacental hemorrhage, narrow therapeutic action, spontaneous abortion, prematurity, and stillbirth.[10] The risk of thrombosis during pregnancy is 4% with warfarin therapy, 9% with UFH during the first trimester, and 33% with only UFH.[11]

In recent years, although LMWH has gained popularity, a revised United States Food and Drug Administration (FDA) report from 2009 did not recommend enoxaparin for thromboprophylaxis in pregnant women with mechanical heart valves.[12] The American College of Cardiology and American Heart Association Guideline recommendation for thromboprophylaxis in pregnant women with a mechanical heart valve is warfarin. If the patient chooses not to take warfarin during the first trimester due to its teratogenic effects, dose-adjusted continuous intravenous UFH or dose-adjusted subcutaneous LMWH is recommended, if the dose of warfarin needed to achieve a therapeutic INR is >5 mg per day. Subcutaneous UFH is not recommended due to the high incidence of valve thrombosis.[8] In our study, we identified four patient groups on varying anticoagulation regimens as shown in Table 2.

Heart valve replacement for women of childbearing age and the decision to use a mechanical valve are still controversial. A bioprosthesis carries the risk of re-operation and early valve deterioration, but

a mechanical heart valve has the disadvantage of indispensable AC.[13] Mihaljevic et al.[14] recommended biological valves for their patient population due to the teratogenic effects of warfarin; however, the freedom from reoperation for biological versus mechanical valves was 79% vs 90% and 38% vs 82% ($p<0.01$) at five and 10 years, respectively.[14] Sbarouni et al.[15] showed that pregnancy accelerated the structural deterioration of a biovalve; however, the outcomes of both valve types were similar. In that study, prematurity and maternal hemorrhagic complications due to heparin were more common in the mechanical heart valve group. A bioprosthesis may be a good choice for women of childbearing age who desire a child; it eliminates the necessity of AC and thus the feto-maternal side effects of such pharmacological treatment, but carries the risk of repeat surgery. In our hospital, all women of childbearing age are counselled on this issue. All patients in our study had mechanical valve implants, as they had all conceived prior to surgery and did not desire any more children.

When we retrospectively reviewed our experience, we also identified four AC regimens. Warfarin was replaced with LMWH (no anti-Xa control) or UFH during the first trimester and two weeks before expected labor in group 1. We observed 35 full-term healthy newborns from 72 pregnancies; however, 18 therapeutic abortions occurred as undesired pregnancies. Many studies have shown healthy newborn rates of 53 to 73%, excluding therapeutic abortions, which is similar to our series.[16] In group 1 (first trimester UFH or LMWH instead of warfarin), the healthy new-born rate is 84%. Nevertheless, 40 babies were born and no congenital anomalies or growth retardation was observed among these infants during follow-up.

The incidence rate of spontaneous abortions is 4.6 to 50% and switching the AC regimen does not dramatically improve fetal outcomes.[17,18] Both medications have deleterious effects by different pathways; however, pregnancy with a mechanical heart valve is precarious. Vitale et al.[19] reported a 37.9% spontaneous abortion rate with warfarin, whereas Salazar et al.[20] reported a rate of 37.5% in patients using subcutaneous UFH. Our spontaneous abortion rate was 16.2% in total, whereas it was 12.5% in the LMWH and UFH group (group 4).

Warfarin provides effective thromboprophylaxis; however, it is also associated with a high rate of prematurity, abortion and embryopathy, known as warfarin embryopathy or fetal warfarin syndrome, when exposure occurs between weeks 6 and 12 of gestation. Warfarin embryopathy manifests mostly in the skeletal system as nasal hypoplasia with deep nasal alar grooves and widespread epiphyseal and vertebral stippling (chondrodysplasia punctate). The cleft lip and/or palate, choanal atresia or stenosis, microphthalmia, optic atrophy, cataracts, malformed ears, coarctation of the aorta, situs inversus, bilobed lungs, ventral midline dysplasia, limb hypoplasia, hydrocephalus, mental retardation, spasticity, and hypotonia have been also reported after in utero warfarin exposure.[21] These fetal effects of warfarin are dose-dependent.[4] The risk of embryopathy is >8% in patients whose warfarin dose is >5 mg per day, compared to <3% in those taking ≤5 mg per day.[7] Warfarin embryopathy varies from 0 to 20% (up to 30%), whereas the estimated risk for malformation is <5%.[4,22] No warfarin embryopathy was observed in our study. This may be due to the fact that none of our patients were on warfarin more than 5 mg per day between weeks 6 and 12 of gestation.

Thromboembolic events have been also reported previously in 4 to 22% of pregnant women treated with LMWH.[23] Thromboembolic complications occurred in 13 (18.1%) pregnancies in our cohort, of which seven (9.7%) were valve thromboses and six (8.4%) were peripheral embolism. No maternal deaths were observed during these pregnancies.

Antepartum and postpartum bleeding is a significant obstetrical complication in pregnant women with mechanical prostheses. McLintock et al.[24] observed antepartum and postpartum bleeding in 17% and 33% of patients with mechanical valves, respectively, and these rates are higher than our results. We observed one bleeding complication (hematoma) in group 1; however, it was due to the patient's misunderstanding of using both warfarin and LMWH before labor. Five patients in group 2 (OAC with ASA) also experienced minor bleeding complications.

In the present study, the healthy newborn rate was 84% in group 1 (first trimester UFH or LMWH). This rate was 12.1% in group 2 (warfarin + ASA group), suggesting that warfarin throughout pregnancy is not feasible due to high rates of abortion, prematurity and morbidity. The healthy newborn rate for group 4 was 62.5%. Surprisingly, the healthy newborn rate was also 62.5% in group 3, suggesting that AC is responsible for most abortions. However, not using AC therapy results in thromboembolic events, leading to high-risk reoperations. Group 4 shows the feasibility of using LMWH; the number of patients in this group may not be sufficient to draw a firm conclusion, compared to groups 1 and 2.

In their study, Saeed et al.[25] reported a prospective observational study indicating the safe administration of enoxaparin throughout pregnancy in 15 patients with mechanical heart valves with respect to anti-Xa levels (1-1.2 U/mL). A randomized-controlled study cannot be performed with this patient profile; therefore, AC regimens are chosen by experts. Gibson et al.[26] reported the failure of weight-based dosing of tinzaparin to achieve therapeutic AC during pregnancy to prevent and treat venous thromboembolic events; however, the clinical results were good and the estimated dose requirement increased with each trimester. In our series, 11 patients with 12 pregnancies using tinzaparin (weight-based dose) gave birth to 10 healthy babies.

On the other hand, a woman with a tricuspid mechanical heart valve had two consecutive pregnancies; one ended in a first trimester spontaneous abortion, and the other was a second trimester therapeutic abortion due to a valve thrombosis. The patient was treated with tissue plasminogen activator.

Recommendations

No consensus exists for the most optimal AC regimen; however, warfarin is the first drug of choice for thromboprophylaxis, and substituting with dose-adjusted UFH or LMWH is reasonable to prevent teratogenicity and reduce the high first-trimester abortion rate. Maternal complications and warfarin embryopathy should be weighed up, when choosing the appropriate AC regimen for mechanical heart valve thromboprophylaxis in pregnant women.

Pregnancy after mechanical heart valve replacement is associated with abortion and maternal thromboembolic complications due to the hypercoagulable state and inadequate AC. New-generation bioprosthetic valves may be used in childbearing-aged women. Adjusting the AC dose with respect to anti-Xa levels may be also advantageous; however, weight-adjusted dosing can also be used for LMWH and UFH.

The AC switching period of one to another carries a high risk for thromboembolic episodes and requires close monitoring. It is not appropriate to administer UFH or LMWH throughout pregnancy, as these two agents carry high abortion rates and are not as effective for thromboprophylaxis as warfarin.

In addition, LMWH is easier to use and monitor and successful pregnancy outcomes usually occur. However, a warfarin dose of ≤5 mg per day throughout pregnancy can be considered an alternative, if the risk of embryopathy is accepted by the woman. It should be emphasized that warfarin provides improved protection for the valve.

Küçüker et al.[27] emphasized the surprisingly high incidence of pregnancy in women with mechanical heart valves. In their pilot study, they also highlighted the major reasons for this issue as insufficient education of the patients regarding the risks of pregnancy and the importance of contraception. It is imperative to conduct a detailed discussion with the patient regarding treatment options prior to commencing treatment.

Limitations of the study

The number of patients in the study may seem limited. However, we believe 57 patients who had a total number of 72 pregnancies is a reasonable number as our clinical experience indicates that most fertile women with a prosthetic heart valve who are being treated with warfarin opt out of pregnancy. Group 1 included three pregnancies in which OAC therapy was replaced with UFH during 6 to 12 weeks and 36 to 38 weeks of pregnancy and group 4 included two women who were treated with UFH throughout their pregnancies. Although these patients' treatment regimens varied from others in their prospective groups, grouping them separately would not allow statistical analysis.

In conclusion, although there is no consensus on the most optimal anticoagulant regimen during pregnancy, substituting warfarin with dose-adjusted unfractionated heparin or low-molecular weight heparin seems suitable to prevent teratogenicity and a high abortion rate in the first trimester. Low-molecular weight heparin is practical to use and can be monitored reliably, resulting in successful pregnancy outcomes. However, warfarin throughout pregnancy ≤5 mg per day may be an alternative choice, if the risk of embryopathy is accepted by the pregnant woman.

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