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Mechanical heart valve prosthesis in pregnancy – multicenter retrospective observational study

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ABSTRACT

Background: Mechanical heart valves carry significant risk during pregnancy.
Aim: To assess the risk of pregnancy and delivery for mother and child in women with mechanical heart valve prosthesis.
Methods: Multicenter retrospective observational study of women with mechanical heart valve prosthesis. The regimen with low molecular weight heparin throughout pregnancy (LMWH) was compared to warfarin since the second trimester (W).
Results: Out of 419 pregnant women with cardiovascular diseases we assessed 14 women with mechanical heart valve prosthesis (3.3%) who experienced 23 pregnancies. There were 13 pregnancies with aortic valve prosthesis, 8 with prosthesis of atrio-ventricular valves and 2 pregnancies with both aortic and mitral valve prosthesis. LMWH regimen was used in 18 pregnancies, W in 5 pregnancies. Major maternal complications occurred in 65% of pregnancies, including 3 strokes and 3 urgent cardio-surgical procedures, all in women with LMWH regimen. Prosthetic valve thrombosis occurred in 26%, all in the LMWH group; no thrombosis was found in W group, ($p = 0.166$). Major bleeding occurred in 30% with no difference between LMWH and W groups ($p = 0.596$). Fetal loss represented 26% of all pregnancies with no difference between LMWH and W group ($p = 1$). The birth weight was not significantly different between LMWH and W groups (2496 ± 327 g vs. 3132 ± 592 g, $p = 0.12$).
Conclusion: The rate of maternal and fetal complications in pregnant women with mechanical valve prosthesis is still high. The anticoagulation regimen using warfarin since the second trimester appears to be the safest one. The best prevention of complications is to avoid the implantation of mechanical valve prosthesis in girls and women in fertile age.

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SOUHRN

Mechanické chlopenní protézy představují v těhotenství významné riziko. Cílem naší práce bylo specifikovat riziko těhotenství a porodu s mechanickou protézou pro matku i dítě. V multicentrické retrospektivní studii byla porovnána léčba nízkomolekulárním heparinem po dobu celého těhotenství (LMWH) s léčbou warfarinem od druhého trimestru (W) u žen s mechanickou chlopenní náhradou.

Výsledky: Mezi 419 těhotnými ženami s kardiovaskulárním onemocněním jsme našli 14 žen s mechanickou chlopenní protézou (3,3 %), u kterých proběhlo celkem 23 těhotenství. Aortální mechanická protéza byla přítomna ve 13 těhotenstvích, mitrální nebo trikuspidální mechanická protéza byla v osmi těhotenstvích a ve dvou těhotenstvích byla současně aortální i mitrální protéza. Režim s LMWH byl zvolen v 18 případech, režim s warfarinem v pěti těhotenstvích. Významné komplikace u matky byly prokázány v 65 %, včetně tří cévních mozkových příhod a tří urgentních kardiochirurgických operací u žen s LMWH režimem. Trombóza mechanické protézy se vyskytla v 26 %, vždy ve skupině s LMWH, ani jednu trombózu jsme neprokázali u žen léčených warfarinem (p = 0,166). Významné krvácení se objevilo ve 30 % bez rozdílu mezi skupinami LMWH a W (p = 0,596). K samovolnému potratu došlo v 26 % bez rozdílu mezi LMWH a W (p = 1). Porodní váha se signifikantně nelišila mezi skupinou s LMWH (2 496 ± 327 g) a warfarinem (3 132 ± 592 g, p = 0,12).

Závěr: Počet mateřských a fetálních komplikací u těhotných žen s mechanickou chlopenní protézou je stále vysoký. Nejbezpečnější se zdá režim užívající warfarin od druhého trimestru. Nejlepší prevencí komplikací těhotenství u žen a dívek s chlopenní vadou je však vyvarovat se implantace mechanické chlopenní protézy ve fertilním věku. Závěrem článku jsou shrnuta současná doporučení pro těhotenství u žen s mechanickou protézou.

Klíčová slova:
Antikoagulace
Mechanická chlopenní protéza
Těhotenství
Trombóza
Vrozená srdeční vada

Mechanical heart valves carry significant risk during pregnancy due to the risk of thrombosis of the prosthetic valve with possible embolisation or heart failure on one hand and the risk of bleeding on the other hand. There is also a fear of the possible embryopathy caused by oral anticoagulants, especially in the first trimester. The options of different anticoagulation regimens during pregnancy are not proved by controlled randomised clinical studies [1,2]. The assessment of the complications during pregnancy with mechanical heart valve is extremely important, because there are more surgical options nowadays on how to avoid implantation of mechanical valve prosthesis in girls or women in fertile age.

Nowadays we can hardly find rheumatic valve disease in young people in our country. The most frequent reasons for the implantation of mechanical heart valve prosthesis are congenital heart diseases (CHDs) and infective endocarditis, which may accompany even mild congenital heart abnormalities, such as bicuspid aortic valve or mitral valve prolapse.

Aim

The aim of our study was to assess the risk of pregnancy and delivery in women with mechanical heart valve prosthesis with different anticoagulation regimens.

Methods

We retrospectively assessed the course of pregnancy and delivery in women with mechanical heart valve prosthesis during the last 5 years. The data were collected from the databases of 3 specialised tertiary referral Centres for adults with congenital heart diseases and from 4 other Cardiovascular centres in University hospitals in different regions of the Czech Republic. We evaluated the type of the heart disease, other important diagnoses, type and position of the prosthesis, anticoagulation treatment and its monitoring during pregnancy, mode of delivery, cardiovascular complications, obstetrical and newborn complications and the rate of abortions and fetal death.

To compare the results between two groups the unpaired T-test, chi-square test and Fisher's exact test were used for categorical variables. Significant difference was considered for $p < 0.05$.

Results

We assessed altogether 23 pregnancies in 14 women with mechanical heart valve prosthesis. Most pregnant women with mechanical prosthesis were found in the databases of the specialised Centres for adults with congenital heart diseases (Table 1). The average age at the time of the first pregnancy was 30.3 ± 5.3 years.

Nine pregnant women had aortic valve prosthesis. The reason for implantation was severe regurgitation or stenosis on bicuspid aortic valve (5×), infective endocarditis (IE) on bicuspid aortic valve (2×), rheumatic aortic stenosis in one woman coming from Asia (1×). One woman with congenital aortic stenosis and IE had both aortic and mitral mechanical valve prosthesis, she also had Leiden mutation. Four women had mechanical mitral valve prosthesis, 2 of them due to residual mitral regurgitation after the operation of incomplete atrio-ventricular septal defect (AVSD) in childhood, 2 due to IE. One woman with congenitally corrected transposition of the great arteries had mechanical atrio-ventricular valve in the systemic right ventricle, one woman with Ebstein anomaly had mechanical valve in tricuspid position. Altogether there were 9 women (15 pregnancies) with mechanical valve in the aortic position (high pressure system) and 6 women (10 pregnancies) with mechanical heart valve in mitral or tricuspid position (low pressure system). Out of them one woman had both aortic and mitral prosthesis and 2 pregnancies. All but one prosthesis were bileaflet, one mitral prosthesis was tilting disc.

The anticoagulation regimen comprised low molecular weight heparin throughout the whole pregnancy (LMWH)

Table 1 – Data from specialised centers for adults with congenital heart disease and other cardiovascular centers.

Centre	Women with CHD	Pregnant women with cardiovasc. disesase	Women in fertile age with mechanical prosthesis	Pregnant women with mechanical prosthesis	Pregnancies with mechanical prosthesis
Homolka, Praha	1352	193	57	8	11
FN Bohunice, Brno	602	203	10	2	4
FN Hradec Králové	354	11	26	1	1
FN Olomouc	18	12	2	1	1
FN Plzeň	?	?	9	1	4
VFN Praha	?	?	?	1	2
FN Motol, Praha	384	?	?	0	0
Altogether	2710	419	104	14	23

in 18 pregnancies (78%), in 2 of them in combination with a low dose of acetylsalicylic acid (50–80 mg). Warfarin (W) was used in 5 pregnancies since the 13th week of pregnancy with frequent assessment of INR. Women treated by W used LMWH with the assessment of antiXa in the first trimester and before delivery.

There were 17 live-born children out of 23 pregnancies (74%). Most deliveries were performed by Caesarean section (88%); there were only 2 planned vaginal deliveries. No embryopathy was referred, 1 baby had a congenital aortic valve disease.

There was no maternal mortality. However, the rate of maternal complications was high. We found only 3 women out of 14 (21%) without maternal complications. Major maternal complications occurred in 65% of pregnancies (Table 2).

Table 2 – Complications in women with mechanical heart valve prosthesis during pregnancy and after delivery.

	N of pregnancies (altogether 23)	% of pregnancies
Major maternal complications	15	65 %
Stroke	3	13 %
Prosthetic valve thrombosis	6	26 %
Cardiac surgery before or immediately after delivery	3	13 %
Bleeding with the need of transfusion or revision	7	30 %
Fetal death/ abortion	6	26 %

Table 3 – Complications in pregnancy according to mechanical valve position and anticoagulation regimen.

	Complications	LMWH N of pregnancies	Warfarin N of pregnancies	*p*
High pressure system – aortic		12*	3	
	Thrombosis	3 (25 %)	0	NS
	Bleeding	3 (25 %)	1 (33 %)	NS
	Fetal loss	1 (8 %)	0	NS
Low pressure system – mitral, tricuspid, CCTGA		8*	2	
	Thrombosis	3 (37.5 %)	0	NS
	Bleeding	2 (25 %)	1 (50%)	NS
	Fetal loss	4 (50 %)	1 (50%)	NS

* One woman had both aortic and mitral mechanical valve prosthesis and 2 pregnancies, the real number of pregnancies was 23.
LMWH – low molecular weight heparin throughout pregnancy.
Warfarin: LMWH in the week 6–12 and before delivery, otherwise warfarin.
CCTGA – congenitally corrected transposition of the great arteries with mechanical valve in atrio-ventricular position in the systemic right ventricle; NS – not significant.

There were 6 valve thrombosis (26%) among 23 pregnancies. All thrombosis developed during the treatment with low molecular weight heparin (LMWH), 5× due to inadequate dose of the LMWH with low antiXa, 1× with adequate dose of LMWH with antiXa (0.8 IU/ml). No valve thrombosis occurred among 5 pregnancies treated by warfarin since the second trimester (p = 0.166) (Table 3, Table 4, Table 5).

Three women experienced valve obstruction requiring acute cardiac surgery during pregnancy (13% of pregnancies), another three valve thrombosis were treated conservatively with heparin or thrombolysis. Three women had ischemic stroke due to valve thrombosis during pregnancy or after delivery.

Gynaecological bleeding requiring transfusion or revision appeared in 7 pregnancies out of 23 (30%) (Table 2). It was present in 2 out of 5 pregnancies treated by warfarin (40%), in 2 out of 2 (100%) of those treated by LMWH with low dose of acetylsalicylic acid (ASA), and in 3 out of 16 pregnancies treated by LMWH only (19%) (Table 5). There was no significant difference in major bleeding between LMWH and W groups (p = 0.596).

Fetal loss or abortion occurred in 6 pregnancies out of 23 (26%). All but one were in women treated by LMWH. We did not find any significant difference in fetal loss between the groups treated by LMWH and warfarin (25% vs. 20%, p = 1). There were two spontaneous abortions in the first trimester, 2 fetal deaths in the second trimester and 2 fetal losses as the probable consequence of cardiac surgery due to valve obstruction. The average birth weight in the "warfarin" and "LMWH throughout pregnancy" groups was 3132 ± 592 g and 2496 ± 327 g, p = 0.12.

Table 4 – Pregnancies with warfarin (W) regimen (N = 5).

N	Prosthesis site	Daily dose of W (mg)	INR	Thrombosis	Bleeding	Stroke	Fetal loss
1	Mitral	12.5	3.5	–	–	–	1
2	CCTGA*	7.5	2.9	–	1	–	–
3	Aortic	4.5	?	–	–	–	–
4	Aortic	10	2	–	–	–	–
5	Aortic	4.5	2–3	–	1	–	––

Table 5 – Pregnancies with low molecular weight heparin (LMWH) regimen (N = 18).

N	Prosthesis site	Daily dose of LMWH (ml)	anti-Xa	Thrombosis	Bleeding	Stroke	Fetal loss
1	Mitral	2× 1ml	0.62–0.69	–	–	–	1
2	Mitral	2× 1ml + ASA 50	0.79	–	1	–	–
3	Mitral	1×?	ND	1	–	–	1
4	Mitral	2× 0.8 ml + ASA 80	ND	–	1	–	–
5	CCTGA*	1× 0.6 ml	0.4	1	–	–	1
6	Tricuspid	2× 0.8 ml	ND	–	–	–	1
7	Mitral + aortic	2× 0.4 ml	ND	–	–	–	–
8	Mitral + aortic	2× 0.4 ml	0.41	1	–	1	–
9	Aortic	2× 0.8–1 ml	0.8	1	–	1	–
10	Aortic	2× 0.6 ml	0.84–0.78	–	1	–	–
11	Aortic	2× 0.6 ml	0.52–0.78	1	1	1	–
12	Aortic	?	?	–	–	–	1
13	Aortic	2× 0.7 ml	0.88	–	–	–	–
14	Aortic	2× 1 ml	0.87	–	1	–	–
15	Aortic	2× 0.6 ml	0.1	1	–	–	–
16	Aortic	?	?	–	–	–	–
17	Aortic	?	?	–	–	–	–
18	Aortic	?	?	–	–	–	–

ASA – acetylsalicylic acid (mg); CCTGA* – mechanical prosthesis in atrio-ventricular position in the systemic right ventricle in congenitally corrected transposition of the great arteries. This patient had two pregnancies with different anticoagulation regimens; LMWH – low molecular weight heparin throughout pregnancy; ND – not done; W – warfarin = LMWH in the week 6–12 and before delivery, otherwise warfarin.

Discussion

Low molecular weight heparin has a stable place in the prevention of thromboembolic events; it can replace warfarin before surgery or before other interventions. Because of no harmful effect to fetus it is often used in pregnancy in different indications. However, the use of LMWH for pregnant women with mechanical valve prosthesis is not recommended by the latest guidelines because of the risk of thrombosis [1].

Although the maternal mortality was zero in our study, the rate of complications was surprisingly high. Almost 80% of all pregnant women with mechanical heart valve prosthesis experienced some kind of maternal complications (at least during one pregnancy), including three urgent cardiac surgical procedures and three strokes.

Thrombosis of the mechanical valve prosthesis during pregnancy was found in 26% of all pregnancies. Valve thrombosis was detected only in those women treated by LMWH throughout pregnancy. No prosthesis thrombosis was found in women treated by warfarin from the second trimester. The small number of women in the warfarin group is probably responsible for the fact, that the difference between the groups was not significant. Very similar rate of mechanical valve thrombosis – 33% – was found in a large review of literature in the "heparin through pregnancy" group [2]. The reason for valve thrombosis in our study was inappropriately low dose of LMWH in all but one patient. In one woman the thrombosis developed during well controlled LMWH treatment with antiXa 0.8 IU/ml. Similar results with thrombotic complications mostly due to sub-therapeutic antiXa levels were referred also by other authors [3]. However, the risk of valve thrombosis was not excluded even with reaching the therapeutic levels of antiXa, similarly to our experience [4,5]. There is a discussion, if the measurements of the pre-dose levels were helpful, with the recommended level of 0.6–0.7 IU/ml [6].

Three surgically treated valve thrombosis in our series resulted in 2 fetal loss. Three valve thrombosis resulted in ischemic cerebral stroke. Even if the difference between the two anticoagulation regimens was not significant due to the small numbers, all valve thrombosis with the subsequent complications were found in the LMWH group, none was in the warfarin group. Our results support the hazard of giving LMWH throughout the pregnancy, in agreement with the new European guidelines [1].

The rate of women treated by LMWH throughout pregnancy was surprisingly high (78%) in our retrospective study. It may be partly explained by the lack of clear information in the previous years. Many cardiologists still historically overestimate the danger of warfarin in pregnancy and underestimate the LMWH risk. The broad use of LMWH in other situations and also in pregnant women without mechanical prosthesis may contribute to the explanation of the LMWH preference.

The rate of maternal bleeding requiring transfusion or surgical revision represented 30% of pregnancies in our study. Similar rate of haemorrhagic complications (17% antenatal and 32% postnatal) were found by other authors [3]. The addition of low-dose acetylsalicylic acid (75–100 mg) to anticoagulation therapy is recommended in high risk patients with mechanical heart valves also in pregnancy, in the second and third trimester, especially in the USA [7,8]. In our study we used the combination of LMWH with low dose of ASA in two women with older types of mitral prosthesis and left ventricular dysfunction. However, both women had bleeding; one of them required hysterectomy after delivery. Using the combination of ASA with anticoagulation we must be aware of the higher risk of bleeding. The other haemorrhagic complications occurred in peripartum while women were on LMWH only. The risk of bleeding could be decreased with the stop of acetylsalicylic acid one week before planned delivery and the use of postpartum intravenous unfractionated heparin (UFH) with aPTT controls until warfarin reaches the therapeutic level. The UFH can be fully reversed by protamin unlike that of LMWH.

Warfarin embryopathy was not found in our study. However, we had no women treated by warfarin between the weeks 6–12. In 5 pregnancies from our series warfarin has been given since the 13th week and was controlled by INR. Warfarin embryopathy is described in the literature in 6.4% of women treated with warfarin throughout the pregnancy, while heparin given from the 6th to the 12th week eliminates this risk substantially [1,2]. The lower dose of warfarin < 5 mg carries lower risk of embryopathy (2.6%) [1]. There was only one bleeding and one fetal loss in our warfarin group without any valve thrombosis or stroke.

The rate of fetal loss was 26% in our series, without significant difference between LMWH and warfarin groups. Our results are in contradiction with another study, where the fetal loss was 70% in women treated by warfarin and 25% in heparin-treated women [9]. However, the numbers in our study are small.

The rate of Caesarean sections was high in our study, mostly due to obstetrician decision. However, vaginal delivery is contraindicated in women treated by warfarin.

The small number of pregnant women with mechanical valve prosthesis (3.3%) in our relatively large series of 2710 women with CHD may be explained by the increasing trend in valve sparing operations of the aortic and mitral valve and also increasing use of bioprosthesis or Ross procedure for women in fertile age. Every effort should be taken to avoid mechanical prosthesis in women who are planning pregnancy.

In conclusion, warfarin seems to be safe concerning valve thrombosis, but it has the risk of embryopathy in the first trimester, especially if the daily dose exceeds 5 mg. It may have a higher rate of fetal loss and stillbirths [9], which was not confirmed by our experience. LMWH throughout pregnancy has definitely a high risk of valve thrombosis, which can be only partly eliminated by keeping the target antiXa. Bleeding complications can be expected in a similar rate in both regimens.

The management of pregnant women with mechanical valve prosthesis is one of the most challenging and difficult subjects. The suggestion of the safest management for mother and child provoked many controversial discussions and even nowadays the recommendations may differ because of the lack of randomised studies. Most data come from smaller observational studies [1–3]. The recommendations in the older guidelines are insufficient [10].

The current recommendations

The new guidelines of the European Society of Cardiology provide the following recommendations [1]:

- Oral anticoagulant treatment should be continued until pregnancy is achieved.
- Continuation of oral anticoagulants should be considered if the dose of warfarin is less than 5 mg a day with a weekly control of INR.
- If the daily dose of warfarin is higher or the mother is not willing to accept a small risk of embryopathy (less than 3%), warfarin is replaced by UFH or LMWH in the weeks 6–12 with the proper weekly control and dose adjustment (aPTT > 2× in UFH or antiXa 0.8–1.2 IU/ml in LMWH 4–6 hours after the application). The importance of the pre-dose level of antiXa above 0.6 IU/ml has not been studied sufficiently.
- Planned delivery is preferred.
- Because of the risk of fetal hemorrhage, warfarin should be withdrawn 2–4 weeks before delivery and switched to heparin or LMWH.
- Delivery should take place in a tertiary centre.
- Vaginal delivery is recommended for women with good function of the heart and valves, without dilatation of the aorta, who take heparin or LMWH.
- Vaginal delivery is contraindicated in women taking warfarin because of the risk of fetal intracranial bleeding.
- Planned Caesarean section may be considered for patients with a high risk of valve thrombosis in order to keep the time without warfarin as short as possible [1].
- The combination of anticoagulation therapy with low dose of ASA [75–100 mg] in the second and third trimester is recommended by the ACC/AHA guidelines [7]. It decreases the risk of thrombosis in high-risk patients, but increases the risk of bleeding.

Our results confirm the abovementioned strategy. However, the best strategy for the future seems to avoid the implantation of the mechanical valves to girls and women in fertile age. If the mechanical valve has already been implanted, these women should get detailed information about the risks of pregnancy and principles of anticoagulation therapy.

Limitations of the study

The number of pregnancies with mechanical valve prosthesis is too low to perform a valuable statistical analysis between the groups with different anticoagulation regimens and different valve position.

The main limitation of our study is that we were probably not able to include all pregnant women with the mechanical heart valve prostheses. We admit there could be a selection bias. The women with uncomplicated pregnancy with mechanical valve prosthesis could have been followed by their local cardiologist and the delivery could have taken place in a local maternity hospital, whereas the complicated or risky patients were more likely to be sent to the centres. However, we checked the databases of specialised centres for adults with congenital heart diseases as well as non-specialised large cardiological centres in different regions of our country. We also asked maternal departments and several local cardiologists, but they were not able to provide us with the data because of the lack of database system. The database of pregnant women with mechanical heart valve prosthesis would be certainly useful. Even with the abovementioned limitations the results are warning.

Conclusion

In spite of regular cardiological controls, we found a high rate of maternal and fetal complications in pregnant women with mechanical heart valve prosthesis. The difference between preventive and therapeutical anticoagulation in pregnancy should be emphasized. The appropriate anticoagulation regimen with frequent controls of anticoagulation activity and dose adjustment is needed. The strategy with LMWH in the first trimester and warfarin since the second trimester seems to be safer with better results than LMWH throughout the whole pregnancy. The best prevention of the complications is to avoid the implantation of mechanical heart valves in girls and women in the fertile age.

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