Correlation between different anticoagulation schemes of pregnant women with mechanical prosthetic heart valves and adverse fetal/neonatal outcomes

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Research Article

Keywords: mechanical heart valve, pregnancy, anticoagulation regimen, fetus/newborn, adverse outcomes

Posted Date: July 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-340670/v2

Abstract

Pregnant women with mechanical prosthetic heart valves (MPHV) have adverse effects on the growth and development of the fetus. Data on MPHV pregnant women and their offspring from our hospital from 2014 to 2020 were retrospectively collected. There were 137 pregnancies, 96 in the warfarin group, 28 in the low-molecular-weight heparin (LMWH) group, 13 in the sequential treatment group. There are 27 cases of spontaneous abortion, 3 cases of stillbirth, 56 live births and 51 artificial abortion. The international normalized ratio (INR, $P < 0.001$), prothrombin time (PT, $P = 0.014$), activated partial thromboplastin time (APTT, $P = 0.035$) of the neonates in the warfarin group were increased compared with the other two groups. Multivariate Tobit regression analysis showed that the probability of spontaneous abortion/stillbirth was positively correlated with INR before delivery (OR 1.13, $P = 0.009$) and valve usage time (OR 1.13, $P = 0.009$). The probability of malformation was positively correlated with worse heart function level (OR 1.20, $P = 0.025$) and INR (OR 1.18, $P = 0.011$) before delivery. The offspring of MPHV pregnant women who continuously take warfarin have poor outcomes and a significantly higher risk of early bleeding. Prenatal consultations for MPHV women should be strengthened to avoid unplanned pregnancy.

Introduction

Studies in the 1980s showed that, hemodynamics during pregnancy will change significantly, blood volume will increase by 45–55%, cardiac output will increase by 30–50%, and heart rate will increase by 10–20 beats per minute [1]. Pregnant women with mechanical prosthetic heart valves (MPHV) may have a heavier heart burden, leading to adverse effects on the growth and development of the fetus. Since 2006, the revised WHO classification has classified this type of pregnant women's risk level as III (medium-high risk) [2]. Lawley, C. M. et al. performed meta-analysis of 256 MPHV pregnant women and reported that the premature birth rate was 25.9% (13.1–41.2%), and the incidence of small for gestational age (SGA) was 14.5% (8-22.5%) [3]. MPHV patients may need lifelong anticoagulation therapy to prevent valve thrombosis. When a woman with this disease becomes pregnant, the anticoagulant treatment becomes more difficult due to the hypercoagulable state of the blood caused by pregnancy.

There are currently three commonly used anticoagulation methods during pregnancy [4]: Vitamin K antagonists (VKA) throughout pregnancy; adjusted-dose twice daily low-molecular-weight heparin (LMWH) throughout pregnancy; subcutaneously inject LMWH from the beginning of pregnancy, until it was changed to VKA from 13 weeks pregnant to the birth. Warfarin has the best anticoagulation effect on MPHV, and its side effects are also outstanding. Not only can it cause fetal nasal and skeletal dysplasia during early pregnancy (0.8% (95% CI, 0.0–1.7%)) [5], but can also cause abnormalities in the second and third trimesters (2.1% (95% CI, 0.1–4.1%)) [5], such as nervous system and ocular malformations; Sriparna Basu [6] reported that even low-dose warfarin therapy can cause fetal bone and nervous system malformations. Batra J [7] et al. reviewed 217 MPHV pregnant women, and found that nearly 2/3 of spontaneous abortions or induced abortions occurred. LMWH does not penetrate the placenta, but the incidence of thrombosis in pregnant women is also significantly higher than that with warfarin (8.7% versus 2.7%) [5]. Therefore, there is currently no optimal anticoagulation solution that is harmless to both pregnant women and fetuses. In addition, most of these studies are carried out by obstetricians and cardiologists. Therefore, there are lack of comprehensive evaluation on neonatal growth and development and various complications, coagulation functions, and prenatal factors have adverse effects on the fetus (spontaneous abortion / stillbirth, deformity, premature delivery, bleeding events).

This study retrospectively included data on 137 pregnancies with MPHV and their fetuses/newborns from our hospital (Beijing Critical Maternal Referral Center) from 2014 to 2020. The growth and development of the latter under different anticoagulation regimens were evaluated, as well as the live birth rate, spontaneous abortion rate, deformity rate, neonatal coagulation function and other indicators. Multi-factor logistic regression was applied to explore the prenatal influencing factors of spontaneous abortion/stillbirth and fetal/neonatal malformation, aiming to improve the prevention and control capabilities in treatments of such high-risk children.

Methods

Study population

This study retrospectively collected data on all MPHV pregnant women (including prenatal examination in our hospital or emergency referrals) and their fetal/newborn children from our hospital (Beijing Critical Maternal Referral Center) from 2014 to 2020. Pregnant women in this study may have one or more mechanical heart valves, excluding biological valves. A total of 105 pregnant women were enrolled, including 137 pregnancies, and were divided into three groups according to different anticoagulant treatment methods during pregnancy: warfarin group, LMWH group, and sequential treatment group. The warfarin group took oral warfarin throughout pregnancy, and discontinued during 36 weeks of pregnancy to the day before childbirth. It was changed to subcutaneous injection of LMWH. In the

LMWH group, LMWH was injected subcutaneously twice a day throughout pregnancy or after finding pregnancy. In the sequential treatment group, LMWH was injected subcutaneously twice a day after pregnancy was found, and it was changed to oral warfarin from the 13th week of pregnancy to the prenatal period. It was discontinued at the earliest to 36 weeks of pregnancy and at the latest to the day before childbirth, and switched to LMWH. The coagulation function was monitored regularly during pregnancy, with a target of INR 1.5-2.5.

Data collection

Electronic medical records were referred to collect data retrospectively, which includes the general condition of pregnant women, such as age, occupation, body mass aindex (BMI), systolic blood pressure, diastolic blood pressure, chronic hypertension, and autoimmune diseases. Heart-related conditions include mechanical valve position, INR before delivery (less than 24 hours), heart function level (New York Heart Association, NYHA), thrombosis or embolism event, bleeding event, arrhythmia, valve usage time (from start to the termination of pregnancy with the current mechanical valve). Obstetrics related information: gestational week, pregnancy times, parity, delivery methods, spontaneous abortion/stillbirth, live births, malformations, premature rupture of membranes, abnormal placenta, postpartum hemorrhage, gestational diabetes, hypertension during pregnancy, preeclampsia, and infection during pregnancy. Pediatric related data: premature infants, birth length, birth weight, small gestational age infants, low birth weight infants, asphyxia, admission to ICU after birth, coagulation function indexes on the first day after birth.

Spontaneous abortion was defined as the spontaneous fetal loss before 28 weeks of gestation. Stillbirth was a baby born following an intrauterine fetal death after 28 weeks 0 days gestation. Preterm birth was defined as delivery before 37 weeks gestation. Low birth weight (LBW): birth weight is less than 2500g. SGA: a newborn whose birth weight is below the 10th percentile of the average body weight of the same gestational age.

Ethical approval

Written informed consent was obtained from all participants and from a parent and/or legal guardian from patients under 18. This study was approved by the Institutional Ethics Committee of Beijing Anzhen Hospital, Capital Medical University and the study was performed in accordance with the Helsinki Declaration.

Statistical analysis

STATA 16.0 statistical software was used to analyze the data. Measurement data conforming to the normal distribution are expressed as mean ± standard deviation, and analysis of variance is used for comparison of multiple groups; count data is expressed as frequency (percentage), and $\chi 2$ test is used for comparison of multiple groups. Pearson correlation analysis was used to analyze the relationship between spontaneous abortion/stillbirth, low birth weight infants, small gestational age infants and different anticoagulant schemes; univariate logistic regression and multi-factor Tobit regression were used to analyze the main influencing factors causing spontaneous abortion/death and malformation. The inclusion of variables in the model was screened according to BIC (Bayesian Information Criterion, BIC). The bilateral test ($\alpha = 0.05$, $P<0.05$) was considered statistically significant.

Results

A total of 105 pregnant women were enrolled in this study, including 137 pregnancies, 96 in the warfarin group, 28 in the LMWH group, and 13 in the sequential treatment group. A total of 27 cases of spontaneous abortion in 3 groups, 3 cases of stillbirth (Table 1), including 23 cases of parous women, 7 cases of primiparas; 26 cases of long-term oral warfarin during pregnancy (6 cases greater than 5 mg, 20 cases less than 5 mg), 4 cases of LMWH only users during pregnancy; 5 cases of gynecological and obstetric diseases (4 cases of endometriosis, 1 case of multiple uterine fibroids), 3 cases of severe infection (1 case of sepsis, 1 case of acute pelvic inflammatory disease, 1 case of acute chorioitis), 1 case of hypothyroidism, 0 cases of NYHA ≥3, 6 cases of multiple spontaneous abortions with unknown causes, 1 case of fetal nervous system malformation, and 1 case of mechanical heart valve replacement during pregnancy. There was 51 artificial abortion.

A total of 8 cases of malformations (5.84%) (4 cases of cardiovascular system, 2 cases of skeletal deformity, 3 cases of nervous system malformation, and 1 case of intestinal malformation) (Table 1).

A total of 56 live births, including 28 cases in the warfarin group, 18 cases in the LMWH group, and 10 cases in the sequential treatment group (Table 2); 53 cases of cesarean section, 3 cases of natural delivery, 7 cases of premature babies, and 5 cases of LBW , 2 cases of SGA, 3 cases of neonatal asphyxia, 5 cases of pulmonary insufficiency, 3 cases of sepsis, 3 cases of neonatal encephalopathy, 18 cases

of blood spots on skin, 2 cases of gastrointestinal bleeding, 5 cases of cranial hematoma, 1 case of disseminated intravascular coagulation, and 13 cases of pathological jaundice. The comparison of the neonatal indicators of the three groups is shown in Table 2. 22 neonates were admitted to the general neonatal ward, 7 were admitted to ICU treatment, and one of them gave up treatment 1 day later. All children admitted to the hospital were monitored for coagulation function. The coagulation indexes of the three groups were compared, and it was found that the INR (P <0.001), PT (P = 0.014), and APTT (P = 0.035) of newborns in the warfarin group were higher than those in the other two groups.

In the offspring of the warfarin group, 7 newborns had significantly increased INR on the first day after birth (2-7.11) (Table 3), which was significantly higher than that of the mother on the same day before delivery (1.1-2.8 fold). Except for 1 case that was changed to LMHW 1 week before delivery, the rest of the cases were withdrawn from warfarin for a short period of time, of which pregnancy was discontinued with 4 cases due to premature rupture of membrane (PROM) and 1 case due to fetal distress with emergency. One case of maternal pregnancy with warfarin dosage > 5mg, 2 cases of maternal pregnancy with acute chorioamnionitis, 1 case with preeclampsia, cardiac insufficiency (grade 3). Of these 7 newborns, 5 were admitted to the general neonatal ward, and 2 were admitted to the ICU (1 premature infant, LBW, with mild asphyxia, respiratory distress syndrome, and gastrointestinal bleeding, gave up treatment 1 day later; 1 case of diagnosed pyaemia, with atelectasis, respiratory failure, encephaledema, gastrointestinal bleeding, discharged after 15 days of treatment).

The dosage of warfarin is 1.5 mg-7.5 mg in the first trimester, with an average of 3.57 ± 1.21 mg. There were 14 cases greater than 5 mg (Table 4). Among the offspring, 1 case was live birth, 4 cases of spontaneous abortion, 1 case of stillbirth, and the remaining 8 cases were medically terminated pregnancy in the first trimester. There were 4 cases of the first pregnancy, with the average age of 26.21 ± 7.39 years old at the time of heart valve surgery (ranging at 19-43 years old).

Using logistics single factor regression analysis, we found that the higher the heart function level and the longer the gestational age, the lower the probability of spontaneous abortion/stillbirth (Table 5), the ORs were 0.35 (0.16, 0.77) and 0.95 (0.91, 0.98), respectively. The higher the INR of the coagulation index before delivery, the higher the probability of spontaneous abortion/stillbirth. The OR was 6.54 (1.30, 33.00). Multi-factor Tobit regression analysis showed that the probability of spontaneous abortion/stillbirth was still negatively correlated with gestational age and positively correlated with the coagulation index INR before delivery (P < 0.05). In addition, the longer the valve usage time, the higher the rate of spontaneous abortion/stillbirth (OR 1.13, P = 0.009).

What's more, it was found that the worse level of cardiac function, the higher the probability of fetal malformation, with the OR of 5.25 (1.51, 18.27) (Table 6). Multi-factor Tobit regression analysis showed that the probability of malformation was not only positively correlated with the worse of cardiac function, but also positively correlated with the coagulation index INR at delivery (P < 0.05).

Table 1 General information of women with different anticoagulant treatment regimens

Index	Warfarin n = 96	Low molecular weight heparin n = 28	Sequential treatment n = 13	*F/H/* χ^2	*P*
Age (years)	32.00±5.68	30.39±3.35	30.85±3.56	1.21	0.302
Occupation				6.91	0.141
Staff	45(46.88)	14(51.85)	11(84.62)		
Farmer	2(2.08)	1(3.70)	0(0.00)		
Others	49(51.04)	12(44.44)	2(15.38)		
Systolic blood pressure	116.66±11.11	116.86±13.55	122.46±10.83	1.45	0.239
Diastolic blood pressure	70.11±7.71	68.43±9.85	71.85±6.91	0.86	0.424
Gestational week	18.07±13.21	27.43±12.80[a]	35.46±6.23[ab]	14.51	**<0.001**
Gravidity	2.90±1.71	2.21±1.03[a]	2.00±1.29[a]	3.38	**0.037**
Parity	0.88±0.73	1.00±0.94	1.23±0.83	1.30	0.277
Mechanical heart valve				3.84	0.698
Mitral valve	43(44.79)	14(50.00)	8(61.54)		
Aortic valve	30(31.25)	7(25.00)	1(7.69)		
Mitral valve and aortic valve	22(22.92)	7(25.00)	4(30.77)		
Cardiac Function				9.20	0.163
1	41(42.71)	7(25.00)	3(23.08)		
2	52(54.17)	18(64.29)	10(76.92)		
≥3	3(3.12)	3(10.71)	0(0.00)		
Thrombotic or embolic events	4(4.17)	2(7.14)	0(0.00)	1.11	0.572
Bleeding event	1(1.04)	2(7.14)	0(0.00)	4.09	0.129
Live birth	28(29.17)	18(64.29)	10(76.92)	18.79	**<0.001**
Stillbirth/Spontaneous abortion	23(23.96)	4(14.29)	3(23.08)	1.20	0.549
Fetal/Newborn Malformation	4(4.17)[c]	3(10.71) [d]	1(7.69) [e]	1.78	0.411
INR before delivery	1.30±0.54	1.11±0.39	1.32±0.73	0.85	0.435
Premature rupture of membranes	6(6.25)	4(14.29)	1(7.69)	1.90	0.387
Abnormal placenta				12.33	0.055
Placenta previa	1(1.04)	0(0.00)	0(0.00)		
Placenta implantation	0(0.00)	1(3.57)	0(0.00)		
Placenta previa and placenta implantation	0(0.00)	2(7.14)	0(0.00)		
Postpartum hemorrhage	1(1.04)	4(14.29)[a]	1(7.69)[ab]	9.46	**0.009**
Gestational diabetes mellitus	3(3.13)	3(10.71)	2(15.38)	4.65	0.098
Pregnancy induced hypertension	3(3.13)	0(0.00)	0(0.00)	1.31	0.519
Chronic hypertension	1(1.04)	1(3.57)	1(7.69)	2.68	0.262
Preeclampsia	2(2.08)	0(0.00)	0(0.00)	0.87	0.648
Infection during pregnancy	7(7.29)	4(14.29)	2(15.38)	1.82	0.403

Autoimmune disease	5(5.21)	7(25.00)[a]	0(0.00)[ab]	12.00	**0.002**
Arrhythmia	7(7.29)	3(10.71)	0(0.00)	1.51	0.471
MPHV usage time (years)	5.78±4.11	7.02±5.02	8.62±4.15	2.98	0.054

[a], significantly different compared with the warfarin group.

[b], significantly different the LMWH group.

[c] Multiple deformities (nose bone loss, complete endocardial pad defect, duodenal atresia) in 1 case, cerebellar vermis missing in 1 case, nasal bone abnormality in 1 case, right ventricle hydrocephalus in 1 case.

[d] Atrial septal defect combined with ventricular septal defect in 1 case, atrial septal defect in 1 case, and ventricular septal defect in 1 case.

[e] 1 case of cerebrovascular malformation.

MPHV: mechanical prosthetic heart valves

Table 2 Comparison of neonates in different anticoagulant treatment groups.

Index	Warfarin n = 28	Low molecular weight heparin n = 18	Sequential treatment n = 10	$F/H/\chi^2$	*P*
Premature delivery	4(14.29)	3(16.67)	0(0.00)	1.80	0.407
Newborn weight (g)	2838.67±643.85	2791.94±528.31	3245.00±372.48	2.31	0.109
Newborn length (cm)	48.90±2.72	48.33±2.95	46.91±10.93[ab]	41.79	**<0.001**
Small for gestational age	0(0.00)	2(11.11)	0(0.00)	4.38	0.112
Low birth weight infant	2(7.14)	3(16.67)	0(0.00)	2.42	0.299
ICU admission	4(14.29)	2(11.11)	1(10.00)	0.17	0.918
Neonatal coagulation index	n = 13	n = 10	n = 6		
INR	3.01±1.83	1.63±0.31[a]	1.64±0.47[a]	25.23	**<0.001**
PT	36.96±23.25	17.80±3.50[a]	17.90±5.67[a]	5.05	**0.014**
APTT	101.00±45.11	71.91±18.74[a]	59.55±20.93[a]	3.81	**0.035**

[a], significantly different compared with the warfarin group.

b, significantly different the LMMH group.

Table 3 Cases of INR > 2 on the first day of newborns in the Warfarin group.

PROM: Premature rupture of membrane

Table 4 Cases with dosage of warfarin greater than 5 mg in early pregnancy

Patient	Neonatal INR	Maternal prenatal INR	Gestational week	Pregnancy comorbidity	Warfarin dosage (mg)	Duration of LMWH treatment post-warfarin
1	3.2	1.63	30	Pre-eclampsia, cardiac insufficiency, fetal distress	3	< 24 hrs
2	3.86	2.06	37	Acute chorioamnionitis, PROM	3	< 24 hrs
3	2	1.7	37	Acute chorioamnionitis	4.875	1 week
4	4	2.93	39	Moderate anemia	4.5	< 24 hrs
5	7.11	2.49	34	Mitral valve neoplasms, PROM	6	< 24 hrs
6	4.9	1.87	36	PROM	2.6	< 24 hrs
7	4.9	1.93	36	PROM	2.6	< 24 hrs

Patient	Age (years)	Age at valve replacement (years)	Valve replacement site	Gestational week	Pregnancy and childbirth history	Warfarin dosage (mg)	NYHA	Complications	Fetal / newborn outcome
1	29	22	MVR	7	G_3P_1	5.25	1	-	Spontaneous abortion
2	34	34	AVR	10	G_5P_3	7.5	2	Marfan syndrome	Abortion
3	29	25	MVR	9	G_3P_1	6.5	2	-	Spontaneous abortion
4	36	26	MVR+ AVR	8	G_4P_0	6.5	1	Endometriosis	Spontaneous abortion
5	34	12	MVR+ AVR	38	G_1P_1	6	2	Preeclampsia, pelvic inflammatory disease, mild pulmonary hypertension	Live birth
6	30	27	MVR+ AVR	11	G_1P_0	6	1	-	Spontaneous abortion
7	26	25	MVR+ AVR	6	G_1P_0	5.25	1	Hypertension during pregnancy	Abortion
8	35	33	MVR	7	G_4P_2	6	1	-	Abortion
9	27	26	MVR+ AVR	7	G_2P_1	6	2	Marfan syndrome	Abortion
10	21	19	AVR	8	G_2P_1	5.25	1	-	Abortion
11	38	29	MVR	8	G_7P_1	6	1	Habitual abortion	Abortion
12	26	20	MVR+ AVR	7	G_1P_0	5.25	1	-	Abortion
13	45	43	MVR+ AVR	9	G_4P_2	5.25	1	-	Abortion
14	32	26	MVR	32	G_4P_0	5.25	1	-	Stillbirth

MVR, mitral valve replacement; AVR, aortic valve replacement; NYHA, New York Heart Association

Table 5 Influencing factors of neonatal spontaneous abortion/stillbirth (single factor, multi-factor)

Index	Single factor		Multi-factor	
	OR (95%CI)	*P*	*OR (95%CI)*	*P*
NYHA	0.35 (0.16, 0.77)	0.009	0.94 (0.85, 1.04)	0.266
Gestational week	0.95 (0.91, 0.98)	0.002	0.95 (0.93, 0.97)	<0.001
Anticoagulation method	0.83 (0.43, 1.59)	0.566	1.02 (0.96, 1.08)	0.575
INR before delivery	6.54 (1.30, 33.00)	0.023	1.14 (1.05, 1.24)	0.003
Number of mechanical valve	1.19 (0.47, 3.01)	0.709	1.02 (0.91, 1.14)	0.779
Mechanical valve usage time (years)	0.82 (0.39, 1.75)	0.615	1.13 (1.03, 1.24)	0.009

NYHA, New York Heart Association

Table 6 Influencing factors of neonatal malformations (single factor, multi-factor)

Index	Single factor		Multi-factor	
	OR (95%CI)	*P*	*OR (95%CI)*	*P*
NYHA	5.25 (1.51, 18.27)	0.009	1.20 (1.03, 1.40)	0.025
Gestational week	1.07 (1.00, 1.14)	0.054	1.03 (0.99, 1.06)	0.151
Anticoagulation method	1.62 (0.64, 4.12)	0.313	1.05 (0.96, 1.14)	0.305
INR before delivery	3.60 (0.98, 13.17)	0.053	1.18 (1.04, 1.34)	0.011
Number of mechanical valve	0.43 (0.05, 3.66)	0.442	0.89 (0.75, 1.05)	0.167
Mechanical valve usage time	0.85 (0.23, 3.21)	0.813	1.03 (0.90, 1.18)	0.677

NYHA, New York Heart Association

Discussion

Spontaneous abortion/stillbirth and warfarin

The hypercoagulable state during pregnancy increases the incidence of valve thrombosis, which can cause acute heart failure and embolism, and increased the mortality rate of pregnant women and fetuses [8,9], therefore, anticoagulation therapy of MPHV pregnant women is crucial. Warfarin is the first choice of anticoagulant drugs for most non-pregnant MPHV patients. And the anticoagulant effect of it in pregnant women is also significantly better than heparin [5,9,10], but it has side effects on the fetus. In the comparison of the three anticoagulation methods in this study, the warfarin group had the lowest live birth rate (29.17%) and the highest stillbirth rate (23.96%), mainly related to warfarin passing through the placenta, which is likely to cause miscarriage and stillbirth [9,11,12]. Compared with the average live birth rate summarized in a meta-analysis in 2017, which was 64.5% (48.8-80.2%) [5], our results are not as expected due to the large gap. That study may have excluded some early pregnancy loss cases [13] , resulting an increased live birth rate. In addition, in our study, the pregnant women in the warfarin group had a smaller gestational week than the other groups (18.07 ± 13.21, $P < 0.001$), and had more pregnancy times than the other groups (2.90 ± 1.71, $P = 0.037$). Considering induced abortion caused by unplanned pregnancy, the live birth rate may have been further "diluted". This is consistent with the report from Batra J [7] (Cardiac Surgery, Mount Sinai Hospital in New York), which have reviewed 217 cases of pregnant women with mechanical valves. Nearly 2/3 of them had spontaneous abortion or artificial abortion. Among aborted fetuses, the rate of induced abortion was as high as 1/3.

In the current study, especially for the 14 cases of warfarin dosage greater than 5 mg in the first trimester, there was only one live birth. Apart from 4 spontaneous abortions and 1 stillbirth, there were 8 cases of artificial abortion in the first trimester. Among them, there were

2 cases of obstetric diseases that were prone to miscarriage, and 2 cases of dominant genetic disease Marfan syndrome, which caused an increase in abortion rate. In addition, these pregnant women are at the gestational age (26.21 ± 7.39 years old) when performing heart valve replacement. Most of the pregnancy (10/14) is not the first pregnancy, suggesting that many cases are unplanned. Owing to insufficient medical consultation before pregnancy and before heart valve replacement, they worried about the side effects of warfarin on the fetus and chose to terminate the pregnancy. The same problem is faced in developed countries. A prospective study in the United Kingdom collected 58 pregnant women with mechanical valves from 2013 to 2015 and found that the prenatal consultation rate was only 51% [4]. There are also some pregnant women who fully understand the condition and side effects of drugs and worry about their own increased risk of thrombosis. They still strongly request that the original warfarin dose not be reduced and continue pregnancy. Although there are international recommendations for anticoagulation during MPHV after pregnancy, it is recommended that warfarin dosages greater than 5 mg should be avoided during early pregnancy [8,14], and that low-dose aspirin should be added during the second and third trimesters to enhance the anticoagulation effect [8,15]. But for unplanned pregnancy, those fetuses have been exposed to high-dose warfarin, and aspirin has also been associated with fetal cleft and early closure of the arterial catheter [16]. In a large multi-center study reported in 2015, 212 MPHV pregnant women were collected, and only 13 patients received aspirin, and the incidence of bleeding was significantly higher than that of pregnant women without aspirin (61.5%: 20.6%, $P = 0.002$) [13].

Fetal malformation and warfarin

Warfarin can cause warfarin embryopathy in the first trimester (6-9 weeks of gestation), which is manifested as nasal bone dysplasia and point-like calcification of the epiphysis. It can also be teratogenic during the second and third trimesters of pregnancy, and is called warfarin fetopathy, which manifests as a central nervous system deformity or ocular deformity [17]. In our study, a total of 8 cases of deformity leads to the incidence of deformity as high as 5.84%. There were 5 cases in the warfarin group and the sequential treatment group, all of which showed warfarin-related malformations (Table 1). In a meta-analysis of 124 MPHV pregnant women in 2015, the average malformation rate of offspring was 8.7% (3.4-16.1%) [3], which is consistent with our findings. In another meta-analysis showing that MPHV pregnant women's progeny deformity rates taking warfarin dosage < 5mg and > 5mg were 2.3% (0.7-4.0%), 12.4% (3.3-21.6%), respectively [5]. This is partially in support of our study as the rate from our data is in between, likely because of the inclusion of several cases of warfarin dosage > 5 mg.

INR of pregnant women before delivery and offspring outcomes

We also demonstrated that the INR of pregnant women before delivery is a risk factor for fetal miscarriage, stillbirth and malformation. Most pregnant women had to oral warfarin anticoagulation therapy with INR closely monitored for the dosage adjustment. Among them, pregnant women who took oral warfarin in the third trimester generally changed to LMWH anticoagulation at least 48 hours before delivery, but sometimes unexpected early delivery or the referral patients will shorten the time to change to LMWH, which causes higher INR at delivery. In addition, unless bleeding or thromboembolic events occur during pregnancy, the pregnant women's INR should also be maintained at a stable level. All these factors make the INR before delivery get closer to the INR during pregnancy, which means that it can better reflect the anticoagulant effect of warfarin during pregnancy, and correspondingly, can also reflect the side effects of warfarin on the fetus.

Warfarin inhibits the vitamin K epoxide reductase that are required for the synthesis of coagulation factors II, VII, IX, and X to achieve anticoagulation. With a half-life of 20-60 hours [18], anticoagulant effect of Warfarin completely disappears 5 to 7 days after drug withdrawal, and coagulation function needs to be closely monitored. Warfarin acts on the fetus by passing through the placenta and still has an anticoagulant effect even after delivery. Because the ability of the liver to combine clotting factors is not yet fully developed, especially for premature babies, making the risk of bleeding in the babies greater than that of pregnant women. In this study, the offspring of warfarin group had 7 cases of INR > 2 on the first day after birth (Table 3). The neonatal INR index was significantly higher than that of the pregnant mother before delivery (1.1-2.8 times), of which 2 cases were admitted to ICU. There were 4 cases of PROM and 1 case of emergency termination of pregnancy due to intrauterine fetal distress. Warfarin had to be discontinued for a short time for those patients, leading to a significantly higher INR in the newborn of the warfarin group than that in other two groups ($P < 0.001$), with also higher risk of bleeding. Furthermore, intrauterine infection can cause fetal/newborn intracranial hemorrhage [19,20]. Of these 7 cases, 2 cases of acute chorioamnionitis also increase the risk of bleeding in the offspring. Therefore, newborns of pregnant women with MPHV, especially those born during the last trimester of oral warfarin, should be transferred to neonatal department as soon as possible to monitor coagulation function avoiding bleeding.

Other factors and offspring outcomes

This study found that pregnant women with longer valve usage time are more prone to spontaneous abortion and fetal death. Given 23 of these 30 cases (spontaneous abortion and fetal death) are all parous, and 26 cases were all oral long-term warfarin during pregnancy, the patients with a long valve usage time may have experienced more pregnancies. For those patients, most of the anticoagulation methods during pregnancy were oral warfarin, so the side effects of the drug caused the increased incidence of spontaneous abortion and stillbirth. Moreover, other factors such as endometriosis, multiple uterine fibroids, and unexplained repeated spontaneous abortion can also increase the rate of spontaneous abortion and stillbirth as the number of pregnancy increases.

Single-factor and multi-factor analysis indicate that both the gestational week in the spontaneous abortion and stillbirth were OR < 1 (Table 5), which means that, the longer the pregnancy time, the lower the rate of spontaneous abortion and stillbirth. A total of 27 cases of spontaneous abortion and 3 stillbirth were included in our study. It is important to screen and prevent anticoagulation related complications after birth, such as intracranial hemorrhage, deformity, although the risk of fetal death in the third trimester is significantly reduced.

MPHV pregnant women have been classified as high-risk [2] in the modified WHO pregnant women's risk stratification. And NYHA ≥ 3 is also classified as a very high-risk factor for adverse outcomes of pregnant women, as well as risk factors such as malformation of offspring [21]. In this study, NYHA was risk factor for fetal malformations in MPHV pregnant women in both single factor regression analysis (OR: 5.25 (1.51, 18.27), P = 0.009) and multifactor regression analysis (OR: 1.20 (1.03, 1.40), P = 0.025). This also suggests that heart function should be actively adjusted before pregnancy and throughout pregnancy to prevent heart failure and reduce the risk of fetal malformations.

It has been nearly 70 years since the world's first artificial mechanical valve surgery [22]. With the continuous development of surgical level and valve technology, more and more MPHV women require fertility. Unplanned pregnancy will not only increase the valve damage [7,23], but also increased the risk of miscarriage and deformity of future generations. In order to minimize this risk, patients should be fully informed that mechanical valve needs life-long anticoagulation treatment before valve replacement, and it has risks to both mother and child. Therefore, biological valves should be recommended under the permission conditions. And it is strongly recommended that patients should consult the opinions of experienced cardiology, obstetrics and pediatricians when preparing for pregnancy, conduct multidisciplinary joint management in tertiary hospitals, choose anticoagulation schemes according to their own conditions (such as valve sites and comorbidities), and avoid unplanned pregnancy at the meantime.

Study limitations

This study is a single-center retrospective study, and the number of cases is limited, so that some neonatal outcomes cannot be statistically compared. Some newborns are not admitted to the pediatric hospital lacking abnormal performance after birth, and the coagulation function test cannot be completed, resulting in biased coagulation index of each group. Our data revealed that INR at delivery is related to fetal prognosis. Because fetal development is dynamic over a period of time and could be affected by many factors, we expect to further investigate the risk of neonatal adverse outcomes due to the dynamic change of coagulation indexes during pregnancy

Conclusion

The overall miscarriage rate and the risk of early neonatal hemorrhage in the MPHV pregnant women are significantly higher than that of the sequential treatment group and LMWH group, and especially those pregnant women who take oral warfarin throughout have the highest rate of spontaneous abortion and stillbirth. For MPHV pregnant women who have a high INR before delivery and a long valve usage time, the offspring are more prone to spontaneous abortion and stillbirth. In addition, poor cardiac function during delivery predicts higher incidence of malformation of offspring. Prenatal consultations should be strongly strengthened for MPHV women of childbearing age, to inform about the risks associated with both pregnancy and offspring, and to avoid unplanned pregnancy at risk.

Abbreviations

MPHV : mechanical prosthetic heart valves

LMWH :low-molecular-weight heparin

INR : international normalized ratio

PT : prothrombin time

APTT : activated partial thromboplastin time

SGA : small for gestational age

VKA: Vitamin K antagonists

BMI : body mass index

NYHA : New York Heart Association

LBW : Low birth weight

PROM: premature rupture of membrane

Declarations

Author contributions

Ziwen Zhao and Guiying Liu contributed to conception and design. All the authors contributed to acquisition and analysis. Ziwen Zhao drafted manuscript. Guiying Liu critically revised the manuscript. All authors reviewed the manuscript and gave final approval.

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