Introduction

Pregnancy is associated with several cardiocirculatory changes that can significantly impact underlying cardiac disease, including an increase in cardiac output, sodium, and water retention leading to blood volume expansion and reductions in systemic vascular resistance and systemic blood pressure. These changes begin early in pregnancy (within the first five to eight weeks), reach their peak during the late second trimester, and then remain relatively constant until delivery. Pregnancy is also a hypercoagulable state, and the risk of thromboembolic complications is higher during pregnancy than at other times. Pregnancy after mechanical heart valve replacement is very risky for both mother and child because of the aggravation of maternal heart function and adverse effects of anticoagulation therapy. Potential risks include maternal heart failure, arrhythmia, infectious endocarditis, and maternal death with advancing gestational age.

ABSTRACT

BACKGROUND: Pregnancy is associated with several cardiocirculatory changes that can significantly impact underlying cardiac disease. These changes include an increase in cardiac output, sodium, and water retention leading to blood volume expansion, and reductions in systemic vascular resistance and systemic blood pressure. In addition, pregnancy results in a hypercoagulable state that increases the risk of thromboembolic complications.

OBJECTIVES: The aim of this study is to assess the maternal and fetal outcomes of pregnant women with mechanical prosthetic heart valves (PHVs).

METHODS: This is a prospective observational study that included 100 pregnant patients with cardiac mechanical valve prostheses on anticoagulant therapy. The main maternal outcomes included thromboembolic or hemorrhagic complications, prosthetic valve thrombosis, and acute decompensated heart failure. Fetal outcomes included miscarriage, fetal death, live birth, small-for-gestational age, and warfarin embryopathy. The relationship between the following were observed:

- Maternal and fetal complications and the site of the replaced valve (mitral, aortic, or double)
- Maternal and fetal complications and warfarin dosage (≤5 mg, >5 mg)
- Maternal and fetal complications and the type of anticoagulation administered during the first trimester

RESULTS: This study included 60 patients (60%) with mitral valve replacement (MVR), 22 patients (22%) with aortic valve replacement (AVR), and 18 patients (18%) with double valve replacement (DVR). A total of 65 patients (65%) received >5 mg of oral anticoagulant (warfarin), 33 patients (33%) received ≤5 mg of warfarin, and 2 patients (2%) received low-molecular-weight heparin (LMWH; enoxaparin sodium) throughout the pregnancy. A total of 17 patients (17%) received oral anticoagulant (warfarin) during the first trimester: 9 patients received a daily warfarin dose of >5 mg while the remaining 8 patients received a daily dose of ≤5 mg. Twenty-eight patients (28%) received subcutaneous (SC) heparin calcium and 53 patients (53%) received SC LMWH (enoxaparin sodium). Prosthetic valve thrombosis occurred more frequently in patients with MVR (P = 0.008). Postpartum hemorrhage was more common in patients with aortic valve prostheses than in patients with mitral valve prostheses (P = 0.005). The incidence of perinatal death was higher in patients with AVR (P = 0.014). The incidence of live birth was higher in patients with DVR (P = 0.012). The incidence of postpartum hemorrhage was higher in patients who received a daily dose of >5 mg of warfarin than in patients who received ≤5 mg of warfarin (P = 0.05). The incidence of spontaneous abortion was also higher in patients receiving >5 mg of warfarin (P ≤ 0.001), while the incidence of live births was higher in patients receiving ≤5 mg of warfarin (P = 0.008). There was a statistically significant difference between the anticoagulant received during the first trimester and cardiac outcomes. Specifically, patients on heparin developed more heart failure (P = 0.008), arrhythmias (P = 0.008), and endocarditis (P = 0.016). There was a statistically significant relationship between heparin shifts during the first trimester and spontaneous abortion (P = 0.003).

CONCLUSION: Warfarin use during the first trimester is safer for the mother but is associated with more fetal loss, especially in doses that exceed 5 mg. The incidence of maternal complications is greater in women who receive LMWH or unfractionated heparin during the first trimester, especially prosthetic valve thrombosis, although the fetal outcome is better because heparin does not cross the placenta.

KEYWORDS: pregnancy, mechanical heart valve

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CORRESPONDENCE: sherifwagdyayad@yahoo.com

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Therapeutic anticoagulation is recommended for all pregnant women with mechanical PHVs (primarily mechanical valves) to prevent valve thrombosis and thromboembolic events.5,6

While warfarin appears to offer the best protection against thromboembolic complications in women with mechanical heart valves, it freely crosses the placenta and is associated with a characteristic embryopathy and an increase in late fetal death and hemorrhagic sequelae.4,7 Embryopathy is most likely to occur with exposure during the first trimester. The teratogenic effects appear to be dose-related, with doses less <5 mg/day providing the highest margin of safety.5,7 Warfarin can be used between the 12th week and 36th week of pregnancy.

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) do not cross the placenta, but require subcutaneous (SC) injections twice daily, and are associated with higher rates of maternal valve thrombosis.10 The available data on UFH and LMWHs are further confounded by the use of subtherapeutic dose regimens or poor patient adherence in many reported cases of valve thrombosis or thromboembolism.11,12

No consensus has been reached regarding the optimal antithrombotic therapy in pregnant patients with mechanical heart valves. Warfarin is contraindicated in pregnancy in North America due to fetal concerns, but European experts have recommended low-dose warfarin (<5 mg daily) throughout pregnancy, given a very low frequency of fetal anomalies. As a result of increasing reports on the use of LMWH, many physicians now use LMWH because of its good safety profile for both mother and baby. However, treatment failures have been reported, and LMWH has not been licensed for use in pregnant patients with mechanical heart valves. Thus, physicians and patients face dilemmas when making decisions on anticoagulation.13

In Egypt, this problem is of particular importance. An unusually large number of women of childbearing age have mechanical valves because rheumatic fever and concomitant valvular heart disease are still common and most severely affect the young.

The risk of complications during pregnancy in a patient with prosthetic heart valve (PHV) depends on the type, position, and function of the valve as well as cardiac function, patient’s symptoms, and functional capacity. Evaluation during pregnancy should include a careful history and physical examination as well as an echo-Doppler study to evaluate cardiac and valvular function. The patient and her family should be advised about the potential complications that might occur during pregnancy, including hemodynamic and symptomatic worsening, a higher incidence of thromboembolism, deterioration of bioprosthetic valves, and potential harm to the fetus due to cardiac medications including anticoagulants (increased rate of fetal loss, prematurity, and fetal growth retardation). Because clinical deterioration often occurs during pregnancy, patients with marked impairment of left ventricular and/or valvular function that are moderately or severely symptomatic (class III and IV) should be advised against pregnancy.14

Aim
The aim of this study is to assess the maternal and fetal outcomes of pregnant females with mechanical PHVs.

Patients and Methods
This is a prospective observational study that included 100 pregnant patients with cardiac mechanical valve prostheses on anticoagulant therapy.

Every patient was subjected to a clinical assessment, including a detailed history with special emphasis on maternal age, anticoagulation regimen, obstetric history, gestational age at delivery, and mode of delivery. The following data relating directly to the current pregnancy were collected: age at conception, cardiac complications, obstetric complications, previous pregnancies, perinatal complications, medication used, regimen of anticoagulation used, results of INRs during the last three months, gestational age at delivery, mode of delivery, and dose of warfarin during previous pregnancies.

Cardiac complications included hospitalization, heart failure requiring treatment, symptomatic documented arrhythmia, endocarditis, cardiac intervention during pregnancy, prosthetic valve thrombosis, thromboembolic and hemorrhagic complications, acute coronary syndrome, and death.

Obstetric complications included intrauterine growth retardation, preeclampsia (pregnancy-induced hypertension and >0.3 g proteinuria in a 24-hour urine sample), eclampsia (preeclampsia with grand mal seizures), premature rupture of membranes (membrane rupture before the onset of uterine contractions), premature labor (spontaneous onset of labor before 37 weeks of gestation), postpartum hemorrhage (during vaginal delivery >500 mL and during cesarean delivery >1000 mL blood loss, or requiring transfusion), and placental abruption (the separation of placenta before the fetus is delivered).

Perinatal complications included fetal death (death after 22 weeks of gestation or weight >500 g), perinatal death (within 30 days postpartum), spontaneous abortion, warfarin embryopathy (eg, facial dysmorphism, hypoplasia of nasal bridge, laryngomalacia, and stippled epiphysis), and other congenital heart anomalies. After birth, gender, birth weight, and Apgar score were recorded.

Other investigations included 12-lead electrocardiogram (cardiac rhythm was recorded whether sinus rhythm or atrial fibrillation), transthoracic echocardiography (to assess the mechanical valve function, left ventricular systolic and diastolic dimensions, and left ventricular systolic and diastolic functions), and transesophageal echocardiography (if needed in the diagnosis of prosthetic valve thrombosis, infective endocarditis, and prosthetic valve dysfunction). This research complied with the principles of the Declaration of Helsinki. All patients gave their written, informed consent to participate in the research, which was approved by the Ethics Committee of the Faculty of Medicine – University of Alexandria.
Results

Site of prosthetic valve(s). A total of 60 patients (60%) had mitral valve replacement (MVR), 22 patients (22%) had aortic valve replacement (AVR), and 18 patients (18%) had double valve replacement (DVR).

Warfarin dosage. A total of 65 patients (65%) received >5 mg of oral anticoagulant (warfarin), 33 patients (33%) received ≤5 mg of warfarin, and 2 patients (2%) received LMWH (enoxaparin sodium) throughout the pregnancy.

Anticoagulants used during the first trimester. A total of 17 patients (17%) received an oral anticoagulant (warfarin) during the first trimester. 9 patients received a daily warfarin dose of >5 mg while the remaining 8 patients received a daily dose of ≤5 mg. In total, 28 patients (28%) received SC heparin calcium and 53 patients (53%) received SC LMWH (enoxaparin sodium). Most of these patients received a dose of 1 mg/kg twice daily. Two patients (2%) received intravenous (IV) UFH.

Mode of delivery. Most patients underwent cesarean deliveries (47 patients), while 24 patients had normal spontaneous vaginal deliveries. Twenty-nine patients experienced spontaneous abortions.

Fetal outcomes. Fifty-two pregnancies (52%) resulted in live births. There were 16 (16%) fetal deaths, 3 (3%) perinatal deaths, and 29 (29%) spontaneous abortions.

Maternal complications according to the site of the replaced valve. Prosthetic valve thrombosis was more common with MVR (Table 1). Postpartum hemorrhage was more common in patients with aortic valve prostheses than in patients with mitral valve prostheses.

Relationship between the site of the replaced valve and fetal outcomes. The incidence of perinatal death was higher in patients with AVR (P = 0.014; Table 2). The incidence of live birth was higher in patients with DVR (P = 0.012).

Relationship between maternal complications and warfarin dosage. The incidence of postpartum hemorrhage was greater in patients who received >5 mg of warfarin daily than in patients who received ≤5 mg (P = 0.05).

Relationship between warfarin dosage and fetal outcomes. There was a significant difference between the dose of warfarin and spontaneous abortion and live births (Table 3).

Relationship between maternal complications and the type of anticoagulant used during the first trimester. There was a significant difference between the anticoagulant received during the first trimester and cardiac outcomes (Table 4).

Relationship between the anticoagulant used during the first trimester of pregnancy and fetal outcomes. There was a significant relationship between heparin shift during first trimester and spontaneous abortion (Table 5).

Discussion

In our study, the most common valve replaced was the mitral valve in 60 patients (60%), followed by AVR in 22 patients (22%) and DVR in 18 patients (18%).

Ashour et al. prospectively gathered data from 100 pregnancies that included 67 women with mechanical valves who were followed up in the prosthetic valve clinic of Cairo University. The authors reported 43 cases of MVR and 12 cases each of AVR and DVR.

Over a 25-year period, Tounsi et al. identified 86 pregnancies that included 57 women with PHVs. There were 34 cases (59.65%) of MVR, 7 cases (12.28%) of AVR, and 16 cases (28.07%) of DVR.

| SITES                        | MVP (n = 60) | AVP (n = 22) | DVP (n = 18) | χ² | MCPp |
|------------------------------|--------------|--------------|--------------|----|-----|
| H.F                          | 8            | 0            | 7            | 11.059 | 0.002 |
| Arrhythmia                   | 5            | 0            | 2            | 2.223 | 0.299 |
| Endocarditis                 | 2            | 0            | 0            | 0.775 | 1.000 |
| Prosthetic valve thrombosis  | 3            | 0            | 5            | 8.978 | 0.008 |
| Emboli                       | 0            | 0            | 0            | –     | –    |
| ACS                          | 0            | 0            | 0            | –     | –    |
| Death                        | 2            | 0            | 1            | 1.176 | 0.547 |
| Intrauterine growth retardation | 2        | 0            | 0            | 5.600 | 0.585 |
| Eclampsia-Preeclampsia       | 0            | 0            | 0            | –     | –    |
| PROM                         | 4            | 3            | 1            | 1.316 | 0.585 |
| Postpartum haemorrhage       | 4            | 7            | 5            | 9.955 | 0.005 |
| Placenta abruption           | 0            | 0            | 0            | –     | –    |

Note: Statistically significant at P < 0.05 by chi-square test. 
Abbreviation: MCP, Monte Carlo significance test.
In our study, 20 patients developed cardiac complications during pregnancy. Fifteen patients developed heart failure (eight patients with MVR and seven patients with DVR). The cause of heart failure was prosthetic valve thrombosis in eight patients. One case required reoperation, three cases received thrombolytic therapy, and five cases were treated with IV UFH. There were three maternal deaths (two patients with MVR and one patient with DVR). Prosthetic valve thrombosis occurred only in the mitral valve position (five of the eight patients were with DVR). Sixteen pregnancies were complicated by bleeding with the most common cause being life-threatening postpartum hemorrhage requiring blood transfusion. The second most common cause of bleeding was the development of a hematoma at the cesarean section incision site. Two cases were complicated by infective endocarditis in mitral valve position.

Our results are in agreement with Ashour et al.13 who studied 100 pregnancies, of which 15 developed maternal complications. There were five maternal deaths. The complications included valve malfunction (thrombosis in eight pregnancies), infective endocarditis in one pregnancy, postpartum hemorrhage (five pregnancies), and bleeding during pregnancy due to placenta previa (one pregnancy). The nine patients who experienced acute valvular obstruction had received heparin in the first trimester, of which five died and four underwent a successful reoperation.

Recently, data from the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC)16 revealed that mechanical valve thrombosis complicated 4.7% of pregnancies with an MHV. In 50% of these patients, the valve thrombosis occurred in the first trimester and all of these patients had been switched to some form of heparin. Hemorrhagic events occurred in 23.1% of patients with MHV.

We studied the effect of the position of the valve and pregnancy outcomes regarding maternal complications and classified the valve positions into three groups: the first was the mitral valve group, the second the aortic valve group, and the third the double valve group. There were no significant differences in the incidence of maternal complications between the groups except for the occurrence of prosthetic valve thrombosis that occurred only with replaced mitral valves. This is consistent with a study by Ashour et al.13 who reported no significant difference in pregnancy outcomes of patients with MVR or AVR, while prosthetic valve thrombosis was more frequent in MVR group.

Shannon et al.17 evaluated patients with mechanical heart valves who required anticoagulation and reported a maternal mortality rate of 1–4%, which is similar to our result of 3%.

### Table 2. Relationship between the site of the replaced valve(s) and fetal outcomes.

| SITES     | MVR (n = 60) | AVR (n = 22) | DVR (n = 18) | TEST OF SIG. | P |
|-----------|--------------|--------------|--------------|--------------|---|
| Abortion  | 20 (33.3)    | 7 (31.8)     | 2 (11.1)     | $\chi^2 = 3.430$ | 0.180 |
| Foetal death | 14 (23.3)   | 1 (4.5)      | 1 (5.6)      | $\chi^2 = 6.009$ | 0.061 |
| Perinatal death | 0 (0.0)     | 3 (13.6)     | 0 (0.0)      | $\chi^2 = 10.956$ | 0.014 |
| Live birth | 26 (43.3)    | 11 (50.0)    | 15 (83.3)    | $\chi^2 = 8.921$ | 0.012 |
| Warfarin embrryopathy | 0 (0.0)     | 0 (0.0)      | 0 (0.0)      | –             | –   |
| Congenital anomaly | 0 (0.0)     | 1 (4.5)      | 1 (5.6)      | $\chi^2 = 3.113$ | 0.152 |

### Table 3. Relationship between warfarin dosage and fetal outcomes.

| WARFARIN DOSAGE | ≤5 (n = 33) | >5 (n = 65) | TEST OF SIG. | P |
|----------------|----------|------------|--------------|---|
| Abortion       | 2 (6.1)  | 27 (41.5)  | $\chi^2 = 13.223$ | <0.001 |
| Foetal death   | 8 (24.2) | 8 (12.3)   | $\chi^2 = 2.282$ | 0.131 |
| Perinatal death| 0 (0.0)  | 3 (4.6)    | $\chi^2 = 1.571$ | 0.469 |
| Live birth     | 23 (69.7)| 27 (41.5)  | $\chi^2 = 6.945$ | 0.008 |
| Warfarin embryopathy | 0 (0.0)  | 0 (0.0)    | –             | –   |
| Congenital anomaly | 1 (3.0)  | 1 (1.5)    | $\chi^2 = 0.244$ | 1.000 |

Note: Statistically significant at $P < 0.05$ by chi-square test. 
Abbreviation: FEP, Fisher’s exact significance test.
In a large contemporary study of 212 women with an MHV, van Hagen et al.\textsuperscript{18} reported a maternal mortality of 1.4%. Furthermore, valve thrombosis and hemorrhagic complications occurred in 4.7% and 23.1% of pregnancies, respectively. Compared to our results, the incidence of maternal mortality and incidence of valve thrombosis were lower and that of hemorrhagic complications was higher, which may in part be a result of the high quality of medical care provided and strict adherence to anticoagulant regimens.

Sillosen et al.\textsuperscript{23} reported two maternal fatalities, both of which occurred in women with mechanical aortic prostheses. The death of a 26-year-old woman was due to hemorrhage, while the other patient died of rapidly progressive and irreversible left-heart failure at 27 weeks of gestation. Again, these authors reported a lower maternal mortality. The cause of death also differed from our study. The discrepancy between our results may be explained by the increased number of cases with an AVR.

**Fetal outcomes.** In total, 52 pregnancies (52%) ended in healthy live births and 29 terminated in abortion (20 patients [33.3%] had MVR, 7 patients [31.8%] had AVR, and 2 patients [11.1%] had DVR). One patient had a therapeutic abortion due to advanced maternal age at 43 years, with a history of Ischemic Heart Disease (IHD) and impaired left ventricle systolic function. Fetal deaths occurred in 16 pregnancies, of which 14 were in women with MVRs. Perinatal deaths occurred in three patients. The first case was due to intracerebral hemorrhage, while the remaining two cases were due to prematurity. Two infants were born with congenital anomalies. Atrial septal defect and tongue-tie were present in one newborn, while the other newborn had cyanotic heart disease. Warfarin embryopathy was not detected in any case.

Our results are in concordance with Ashour et al.\textsuperscript{13} who found that of the 100 pregnancies in the study group, 56 resulted in healthy births. Fetal loss occurred in 44 pregnancies due to spontaneous abortions in the first trimester (28); intrauterine fetal death (4); stillbirth (3), including twins who died of warfarin embryopathy; neonatal death due to meconium aspiration (1); premature birth (2); Rh incompatibility (2); and preterm death of the mother (4). van Hagen et al.\textsuperscript{18} found that women with a mechanical heart valve had only 58% chance of

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### Table 4. Relationship between the anticoagulant used during the first trimester and cardiac complications.

| Anticoagulant Used During 1st Trimester | Heart Failure | Arrhythmia | Endocarditis | Prosthetic Valve Thrombosis | Thromboembolic | Endocarditis | Prosthetic Valve Thrombosis | Thromboembolic | Endocarditis | Prosthetic Valve Thrombosis | Thromboembolic |
|--------------------------------------|---------------|-------------|--------------|-----------------------------|----------------|--------------|-----------------------------|----------------|--------------|-----------------------------|----------------|
| Warfarin (n = 17)                    | 1 (5.9)       | 0 (0.0)     | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        |
| Heparin Calcium (n = 28)             | 9 (32.1)      | 5 (17.9)    | 1 (3.6)      | 4 (14.3)                    | 0 (0.0)        | 4 (14.3)    | 0 (0.0)                     | 0 (0.0)        | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        |
| Enoxaparin Sodium (n = 53)           | 4 (7.5)       | 1 (1.9)     | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        |
| Unfractionated Heparin (n = 2)       | 1 (50.0)      | 1 (50.0)    | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        | 0 (0.0)      | 0 (0.0)                     | 0 (0.0)        |

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### Table 5. Relationship between the anticoagulant used during the first trimester of pregnancy and fetal outcomes.

| Anticoagulant Used During 1st Trimester | Spontaneous Abortion | Foetal Death | Perinatal Death | Live Birth | Warfarin Embryopathy | Congenital Anomaly |
|--------------------------------------|----------------------|-------------|-----------------|-----------|----------------------|-------------------|
| Warfarin (n = 17)                    | 11 (64.7)            | 2 (11.8)    | 0 (0.0)         | 4 (23.5)  | 0 (0.0)              | 0 (0.0)           |
| Heparin Calcium (n = 28)             | 5 (17.9)             | 7 (25.0)    | 0 (0.0)         | 16 (57.1) | 0 (0.0)              | 1 (3.6)           |
| Enoxaparin Sodium (n = 53)           | 12 (22.6)            | 7 (13.2)    | 3 (5.7)         | 31 (58.5) | 0 (0.0)              | 1 (1.9)           |
| Unfractionated Heparin (n = 2)       | 1 (50)               | 0 (0.0)     | 0 (0.0)         | 0 (0.0)   | 0 (0.0)              | 0 (0.0)           |

| Test of Sig. | \( \chi^2 \) | MCp |
|--------------|--------------|-----|
| Spontaneous abortion | 13.684 | 0.003 |
| Foetal death | 2.270 | 0.565 |
| Perinatal death | 2.743 | 0.614 |
| Live birth | 6.715 | 0.053 |
| Warfarin embryopathy | 0.744 | 1.000 |
| Congenital anomaly | 13.684 | 0.003 |

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experiencing an uncomplicated pregnancy resulting in a live birth, which is consistent with our findings that a healthy live birth occurred in 52% of the study population.

Chan et al. stated that the risk of early abortion clearly exceeded 20%. The incidence of all-cause congenital malformations was higher (14%, or six offspring). Only one live birth was reported to have evidence of warfarin embryopathy with an overall incidence of 8%. Although the abortion rates were similar, the incidence of congenital anomalies and warfarin embryopathy differed perhaps because the diagnoses were based on autopsies.

**Maternal complications according to warfarin dosage.**

The patients were divided into two groups. Group 1 (n = 33) achieved their target INR during pregnancy with ≤5 mg/day of warfarin. Group 2 (n = 65) achieved their target INR during pregnancy with ≥5 mg/day of warfarin.

In group 1, two patients (6.1%) had a spontaneous abortion. Hemorrhagic complications occurred in 2 patients (6.1%), 8 pregnancies (24.4%) resulted in fetal deaths, and 23 pregnancies ended in live births (69.7%).

In group 2, 27 patients (41.5%) had a spontaneous abortion. Five pregnancies were complicated by intrauterine growth retardation (7.7%). Fetal deaths occurred in 8 patients (12.3%), 14 patients (21.5%) had hemorrhagic complications, and 27 pregnancies ended in live births (41.5%).

Tounsi et al. showed an association between the dose of oral anticoagulant and adverse effects. A warfarin dose of >5 mg is associated with adverse effects.

Samiei et al. suggested that the risk is probably lower if ≤5 mg of warfarin is prescribed and, furthermore, that a low dose of warfarin during pregnancy is overall safe with minimal fetal-maternal complications.

Mazibuko et al. found no congenital fetal anomalies in 29 (50%) patients on ≤5 mg of warfarin during the first trimester. Furthermore, the four (7%) cases of embryopathies occurred in women who were taking >5 mg of warfarin daily.

Vitale et al. suggested that there was a close association between warfarin dosage and fetal complications in pregnant women with mechanical PHV. These investigators studied 58 pregnancies and showed that the majority of fetal complications were related to warfarin dose of >5 mg daily. A total of 33 gestations in women taking <5 mg of warfarin resulted in 28 healthy babies (82%) in comparison with 22 fetal complications (fetal loss 76% and warfarin embryopathy 8%) that occurred in 25 women treated with >5 mg of warfarin daily. The same group of investigators later reported poor outcomes in 30 of the 71 pregnancies (fetal loss in 28 cases and embryo wastage in 2 cases).

Sadler et al. reported seven miscarriages in 11 women treated with >5 mg of warfarin daily compared to five miscarriages in 11 women treated with ≤5 mg of warfarin daily.

We also found that the women who received >5 mg warfarin per day had more fetal complications.

Mazibuko et al. reported a greater incidence of warfarin embryopathy in patients who received warfarin during the first trimester. However, not all of our patients received warfarin during the first trimester. McLintock et al. reported two perinatal deaths and two stillbirths resulting from fetal intracerebral hemorrhage in women taking warfarin at doses of 4 mg/day and 5 mg per day, respectively, and another infant death due to warfarin embryopathy in a woman taking 6 mg per day until 34 weeks of gestation. The previous result differs from our findings. This may be because the fetal intracerebral hemorrhage may have resulted from an increased INR independent of the warfarin dosage.

**Maternal complications according to the anticoagulant used during the first trimester of pregnancy.**

The patients were divided into three groups according to the anticoagulant used during the first trimester: group 1 (17 patients) received oral anticoagulant (warfarin), group 2 (53 patients) received LMWH (enoxaparin), and group 3 (30 patients) received heparin (SC heparin calcium or IV UFH).

Our results are in concordance with Ashour et al., Geelan et al., Samiei et al., Tounsi et al., and Khamooshi et al., regarding the lower rate of maternal complications in women receiving warfarin in the first trimester and the higher rate of prosthetic valve thrombosis in women receiving LMWH or UFH during the first trimester. With the exception of Tounsi et al., our results are also similar with regard to fetal outcome in the heparin group, with live births occurring in 50–60% of pregnancies. Tounsi et al. reported a higher rate of live births, which may be in part due again to the high-quality medical follow-up provided and strict adherence to anticoagulant regimens.

Contrary to their results, we noted a higher rate of spontaneous abortions and fewer live births in women receiving warfarin during the first trimester. This may explain by the fact that 52% of our patients in this group received high doses of warfarin.

Ashour et al. and Samiei et al. reported 52% and 60.5% live births, respectively, in the group receiving warfarin during the first trimester. These results are similar to our finding of 50% live births in the group of women who received ≤5 mg of warfarin daily.

Similarly, data from Sillesen et al. confirmed that fetal complications primarily involved increased numbers of miscarriages and growth restriction that is possibly linked to the use of vitamin K antagonists. However, warfarin embryopathy was only observed in a few patients on continued high-dose warfarin.

Recently, data from the European Society of Cardiology ROPAC revealed that the use of vitamin K antagonists compared to heparin in the first trimester was associated with a higher rate of miscarriage (28.6% versus 9.2%, P < 0.001) and late fetal death. Similar to our findings, warfarin embryopathy was very rare.

**Conclusion**

Maternal complications are higher in valves in mitral position, in particular valve thrombosis, although the position...
of the prosthetic valve does not significantly influence fetal outcomes.

Women receiving >5 mg of warfarin daily are more susceptible to hemorrhagic complications and fetal loss.

Warfarin in the first trimester is safer for the mother but is associated with more fetal loss especially if the dose exceeds 5 mg daily.

Maternal complications are more frequent in women receiving LMWH or UFH during the first trimester, in particular prosthetic valve thrombosis. However, fetal outcomes are better because heparin does not cross the placenta.

Author Contributions
Conceived and designed the experiments: SWA, MH, EAM, AG. Analyzed the data: SWA, MH, EAM, AG. Wrote the first draft of the manuscript: SWA, MH, EAM, AG. Contributed to the writing of the manuscript: SWA, MH, EAM, AG. Agree with manuscript results and conclusions: SWA, MH, EAM, AG. Jointly developed the structure and arguments for the paper: SWA, MH, EAM, AG. Made critical revisions and approved final version: SWA, MH, EAM, AG. All authors reviewed and approved of the final manuscript.

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