INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH AND INNOVATIVE STUDIES
ISSN: 2820-7157
www.ijsrisjournal.com

August 2025 Volume 4 Number 4 193-196

Received Date: July 19, 2025 Accepted Date: August 11, 2025 Published Date: August 30, 2025

The Effect of Warfarin Dosage on Maternal and Fetal Outcomes in Pregnant Women with Prosthetic Heart Valves: A Comprehensive Review

Alia Ali Atiya Al-Bouabdi [1], Zainab Ali Alshobani [2], Jalilah Salman Althuwaini [2], Hussain Abdrabalameer Albahrani [2], Muna Abdullah A Alayald [3], Fatimah Nassir Al Haddad [4], Ayman Abdullah Alzain [5], Wafaa Hussein Al Sagar [6], Jehan Fahad Shinwan Alanazi [7], Roaa Ahmed Ali Alghamdi [7], Laila Mohd Mosa Al Hadari [8], Yahya Ali Alabood [9], Manal Mohsen Atiyah [10], Aziz Mohammed Saleh Albalawi [11], Alanazi, Hamoud Hazim R [11], Hussain Abdullah Alturaiki [12]

1. Genetic Blood Diseases Center
2. Prince Saud Bin Jalawi Hospital
3. AlOmran Health Center
4. Abdulaziz bin Sulaiman Alafaliq for tumor early detection and diagnosis center
5. KING FAISAL GENERAL HOSPITAL
6. MCH hospital Al HASA
7. King Abdulaziz University Hospital
8. Maternity and children hospital Alahsa
9. ALjafr General Hospital.
10. King Khalid Hospital
11. Comprehensive Specialized Clinics for Security Forces in Tabuk
12. Border guard medical center in Riyadh

Abstract

The management of anticoagulation in pregnant women with mechanical prosthetic heart valves (PHVs) poses a significant clinical challenge, requiring a balance between preventing life-threatening maternal thromboembolism and minimizing fetal harm. Warfarin, the most effective anticoagulant for valve protection, is teratogenic and associated with adverse fetal outcomes. This review synthesizes current evidence demonstrating that daily warfarin dosage is a critical factor stratifying these risks. High-dose warfarin (>5 mg/day) is

associated with a substantially elevated risk of fetal warfarin embryopathy (up to 12.4%) and pregnancy loss. In contrast, low-dose warfarin (≤5 mg/day) carries a markedly lower risk of embryopathy (approximately 1.5%) and offers superior maternal thromboembolic protection compared to heparin-based regimens. Current guideline recommendations are therefore stratified by dose, favoring continued warfarin use throughout pregnancy for women maintained on ≤5 mg/day, while considering first-trimester heparin substitution for those requiring >5 mg/day. This review underscores the necessity for individualized, multidisciplinary management and informed shared decision-making, highlighting warfarin dosage as a pivotal element in optimizing outcomes for both mother and fetus.

1. Introduction

Pregnancy in women with mechanical prosthetic heart valves (PHVs) is associated with high maternal and fetal risks. The hypercoagulable state of pregnancy significantly increases the risk of valve thrombosis, systemic embolism, and maternal mortality (1). Warfarin, a vitamin K antagonist (VKA), provides the most effective protection against these thromboembolic events but readily crosses the placenta, posing risks of teratogenesis, fetal wastage, and hemorrhage (2). This creates a profound therapeutic dilemma. Over the past two decades, evidence has coalesced around the daily maintenance dose of warfarin as a key determinant of fetal risk, allowing for more nuanced risk stratification and management. This comprehensive review examines the effect of warfarin dosage on maternal thromboembolic outcomes and fetal complications, and its implications for clinical practice.

2. Pathophysiology and the Clinical Dilemma

Mechanical PHVs mandate lifelong therapeutic anticoagulation. Pregnancy induces a hypercoagulable state through increased levels of clotting factors (I, VII, VIII, X), decreased protein S, reduced fibrinolysis, and venous stasis (1). This elevates the risk of valve thrombosis—a catastrophic event with mortality rates exceeding 20% (3). While heparins (unfractionated heparin/UFH and low-molecular-weight heparin/LMWH) do not cross the placenta and are safer for the fetus, meta-analyses consistently demonstrate their inferior efficacy in preventing maternal thromboembolism compared to warfarin in this population (4, 5). The core conflict lies in warfarin's high efficacy for the mother versus its potential for causing fetal warfarin syndrome (embryopathy) with first-trimester exposure and fetal intracranial hemorrhage with later exposure.

3. Warfarin Dosage and Fetal Outcomes

The relationship between warfarin dose and specific fetal complications is well-established.

- **Embryopathy and First-Trimester Loss:** Exposure between gestational weeks 6 and 12 can cause fetal warfarin syndrome, characterized by nasal hypoplasia, stippled epiphyses, and ocular abnormalities. A seminal systematic review by Chan et al. (6) demonstrated a stark dose-dependency: the pooled incidence of embryopathy was 12.4% with a mean warfarin dose >5 mg/day, compared to only 1.5% with a dose ≤5 mg/day. Spontaneous abortion rates were also significantly higher in the high-dose group (6). Subsequent studies have reinforced this ≤5 mg/day threshold as a marker of significantly lower embryopathic risk (7).

- **Later Fetal Complications:** Warfarin use in the second and third trimesters is associated with an increased risk of fetal central nervous system abnormalities (e.g., ventriculomegaly, Dandy-Walker malformation) and hemorrhage. The risk of fetal intracranial hemorrhage, particularly during the trauma of delivery, persists throughout pregnancy. While the dose relationship for later-term fetopathy is less quantified than for embryopathy, higher levels of anticoagulation logically increase hemorrhage risk (8).

- **Overall Pregnancy Loss:** The pooled fetal loss rate (spontaneous abortion and stillbirth) is significantly greater with high-dose warfarin. Chan et al. reported rates of 33.6% with warfarin >5 mg/day versus 20.2% with warfarin ≤5 mg/day (6).

4. Warfarin Dosage and Maternal Outcomes

Maternal thromboembolic risk is primarily related to the intensity and consistency of anticoagulation, reflected by the time in therapeutic range (TTR). However, the absolute warfarin dose influences clinical management strategies, which in turn affect maternal risk.

- **Warfarin Throughout Pregnancy:** Maintaining therapeutic warfarin (INR target typically 2.5-3.5, depending on valve type and position) for the entire pregnancy provides the strongest protection for the mother. D'Souza et al. (4), in a large meta-analysis, found the lowest pooled incidence of maternal thromboembolism with this approach (2.7-3.7%).

- **Heparin Substitution Strategies:** For women on >5 mg/day, guidelines often propose substituting warfarin with dose-adjusted UFH or LMWH during the first trimester (weeks 6-12) to avoid embryopathy. This "switch strategy," while reducing fetal risk, increases the maternal risk of thromboembolism during the substitution period. Studies show thromboembolic rates of 8-9% with such heparin use in the first trimester (4, 5). Therefore, the maternal benefit of continuing warfarin must be weighed against the increased fetal risk at higher doses.

5. Guideline Recommendations Stratified by Dose

Contemporary guidelines from major cardiology societies incorporate warfarin dose into their recommendations (9, 10, 11):

- **For women requiring ≤5 mg/day warfarin:** Continuing warfarin throughout pregnancy is a reasonable option (Class IIa/IIb), given the lower fetal risk and optimal maternal protection. Careful INR monitoring and dose adjustment are mandatory.

- **For women requiring >5 mg/day warfarin:** Strategies involving replacement of warfarin with dose-adjusted LMWH or UFH during the first trimester (weeks 6-12) and close to term are generally recommended (Class IIa) to mitigate the high risk of embryopathy and delivery-related fetal hemorrhage. Warfarin is used during the second and early third trimesters.

- **Universal Recommendations:** All guidelines stress: 1) the need for multidisciplinary care in specialized centers, 2) meticulous anticoagulant monitoring (anti-Xa activity for LMWH), and 3) exhaustive patient counseling on absolute risks to facilitate informed, shared decision-making.

6. Conclusion and Future Perspectives

The management of anticoagulation in pregnant women with mechanical PHVs remains high-risk. The daily maintenance dose of warfarin is a crucial prognostic factor: doses ≤5 mg/day are associated with an acceptable fetal risk profile and superior maternal efficacy, supporting warfarin continuation. Doses >5 mg/day significantly elevate the risk of fetal embryopathy and loss, justifying consideration of heparin substitution in sensitive periods despite the associated increase in maternal thrombotic risk.

Future improvements await the development of safer, equally effective anticoagulants. Direct oral anticoagulants (DOACs) are currently contraindicated in patients with mechanical valves. Until novel therapies emerge, a dose-stratified approach to warfarin, guided by rigorous monitoring and shared decision-making within a multidisciplinary team, represents the standard of care for optimizing outcomes in these complex pregnancies.

References

1. Elkayam U, Goland S, Pieper PG, Silverside CK. High-risk cardiac disease in pregnancy: part I. J Am Coll Cardiol. 2016 Aug 2;68(4):396-410.

2. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3 Suppl):627S-44S.

3. Van Hagen IM, Roos-Hesselink JW, Ruys TP, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation. 2015 Jul 14;132(2):132-42.

4. D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. Eur Heart J. 2017 May 14;38(19):1509-1516.

5. Steinberg ZL, Dominguez-Islas CP, Otto CM, Stout KK, Krieger EV. Maternal and Fetal Outcomes of Anticoagulation in Pregnant Women With Mechanical Heart Valves. J Am Coll Cardiol. 2017 Jun 6;69(22):2681-2691.

6. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med. 2000 Jan 24;160(2):191-6.

7. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol. 1999 May;33(6):1637-41.

8. Basude S, Hein C, Curtis SL, Clark A, Trinder J. Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: What are the risks? A retrospective

observational study. BJOG. 2012 Jul;119(8):1008-13.

9. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018 Sep 7;39(34):3165-3241.

10. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e72-e227.

11. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018 Nov 27;2(22):3317-3359.