Journal of Cardiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

The effectiveness and side effects of anti-coagulant drugs in pregnant women with mechanical or bio-prosthetic heart valves: A systematic review and meta-analysis study

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ARTICLE INFO

Article history:
Received 3 December 2024
Received in revised form 16 July 2025
Accepted 8 August 2025
Available online xxxx

Keywords:
Anticoagulant therapy
Pregnancy
Prosthetic valves
Warfarin
Low molecular weight heparin

ABSTRACT

Background and objectives: Patients with pregnancy and mechanical or bio-prosthetic heart valves (BHVs) need tailored antithrombotic therapy to prevent thromboembolism. The goal of this study was to evaluate the effects and complications of various anticoagulation strategies used during pregnancy in these patients using a meta-analysis. *Method:* We searched PubMed, Google Scholar, Scopus, EMBASE, and Web of Science databases and discovered 24 articles. We also discarded some articles when evaluating them in detail due to inadequate information. Finally, 24 studies were included in the systematic review. We compared pregnancy outcomes in three groups of pregnant women: 1) Those taking warfarin; 2) Those taking LMWH (Low Molecular Weight Heparin) or UFH (Unfractionated Heparin); 3) Those on no anticoagulant therapy. The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study. The ethic code is: IR.SBMU.RETECH.REC.1403.831. *Results:* The incidence of maternal thromboembolic events was higher in the UFH or LMWH group, but fetal complications (FC) were lower in this group. Using warfarin during the first trimester was associated with a higher abortion rate, embryopathies, and FCs overall. Using <5 mg of warfarin daily to maintain their targeted INR had a lower risk of developing. Preterm labor and spontaneous abortion were observed in 0.09 (95 % CI = 0.04–0.14) and 0.08 (95 % CI = 0.01–0.14) of cases in the LMWH/UFH subgroup. In terms of maternal complications (MCs) in Warfarin subgroup, maternal hemorrhagic complications, maternal thromboembolic events, and valve thrombosis were respectively observed in 2.0 (95 % CI = 0–3), 0.01 (95 % CI = 0.00–0.03), 0.01 (95 % CI = 0.00–0.03); in LMWH subgroup the rates were 0.18 (95 % CI = 0.09–0.27), 0.03 (95 % CI = 0.00–0.06), and 0.28 (95 % CI = 0.15–0.71); and finally in those taking no anticoagulant therapy, the rates were 0.02 (95 % CI = 0.03–0.06), 0.07 (95 % CI = 0.06–0.19).

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https://doi.org/10.1016/j.jjcc.2025.08.002

Please cite this article as: M.I. Shishesaz, R. Eshraghi, A. Bahrami, et al., The effectiveness and side effects of anti-coagulant drugs in pregnant women with mechanical or bio-..., Journal of Cardiology, https://doi.org/10.1016/j.jjcc.2025.08.002

Conclusions: According to the results, preterm labor is a significant fatal complication in pregnant women on warfarin. Maternal hemorrhagic complications and thromboembolic events occur in the LMWH subgroup. There are no significant differences in other complications between the three subgroups.

Introduction

Pregnancy, a hypercoagulable state, is a critical period for women with mechanical heart valves (MHV), as it presents unique challenges in managing their cardiovascular health [1]. There are some conditions where pregnant women are at greater risk of thromboembolic complications (TECs) [2]. One of the high-risk conditions is MHV replacement. Pregnant women with MHVs have a chance of only 58 % of uncomplicated pregnancy with live births [3]. The primary objective of anticoagulant therapy in pregnant women with MHVs is to minimize the risk of valve thrombosis and thromboembolic complications while ensuring the developing fetus's safety. The anticoagulant of choice for the general patient population with MHVs is vitamin K antagonists (VKAs) such as warfarin, as recommended by guidelines [4]. Although VKAs have the lowest risk of maternal complications (MCs), the use of VKAs during pregnancy is associated with an increased risk of embryopathy, particularly during the first trimester [4].

VKAs, low molecular weight heparin (LMWH), and unfractionated heparin (UFH) or a combination of the medications are recommended to be taken into the anticoagulation regimens during pregnancy in patients with MHVs [4,5]. The risks of fetal complications (FCs) following the use of LMWH and UFH in the first trimester are lower than with VKAs, considering that neither LMWH nor UFH crosses the placenta. However, some studies included the potential risks of using LMWH and UFH, such as heparin resistance and allergy, which manifest limitations in their use [5]. UFH is also reported to be associated with more thrombotic risks than LMWH [6]. A few systematic reviews or meta-analysis studies have been conducted on this topic; However, either they have studied a more limited range of FCs or MCs or the study has not discussed the outcomes systematically [7–10]. In this study, we performed a systematic review and meta-analysis to assess the benefits and potential risks of VKAs and heparin anticoagulation in both the fetus and the mother. Additionally, we assessed the data providing the location of the prosthetic valve in each patient.

Methods

This systematic review and meta-analysis study was performed in compliance with the revised standards of the Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. The PRISMA checklist is included in Online Tables 1 and 2. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42025616175.

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study. The ethic code is: IR.SBMU.RETECH.REC.1403.831. (Grant Number: 43009152).

Literature search

We conducted a comprehensive search in databases, including PubMed, Scopus, Web of Science (WoS), and Embase from the inception to January 2024. Relevant articles were identified using the keywords: “warfarin”, “heparin”, “anticoagulant”, “pregnant”, “infant”, “bioprosthetic heart valve”, and “mechanical heart valve” along with their equivalents and specific related Emtree and MeSH terms. The detailed search strategy is provided in Online Table 3. We then screened the reference lists of each retrieved paper and extracted related citations.

Inclusion and exclusion criteria

We included studies involving pregnant women with MHVs or bioprosthetic heart valves (BHVs) reporting maternal outcomes (e.g. thromboembolic events, hemorrhagic complications, valve thrombosis) and/or FCs (e.g., embryopathies, low birth weight, neonatal death, preterm labor, spontaneous abortion, stillbirth). We excluded non-English publications, narrative or systematic reviews and meta-analyses, and studies with inadequate data.

Data management and screeningly

After the removal of the duplicates using EndNote Reference Management Software, we initially screened the titles and abstracts and then reviewed the full texts of relevant studies. Two independent reviewers (RH and AT) conducted the initial screening, with conflicts resolved by a third reviewer (RE).

Data extraction

Two independent reviewers (RH and AT) assessed the full text of the included studies and extracted the data, along with assessing the quality of the included studies. All data regarding the demographics and baseline characteristics of patients (e.g., gender, age, and country), study characteristics, MCs of anticoagulants, and fatal complications of anticoagulants were extracted.

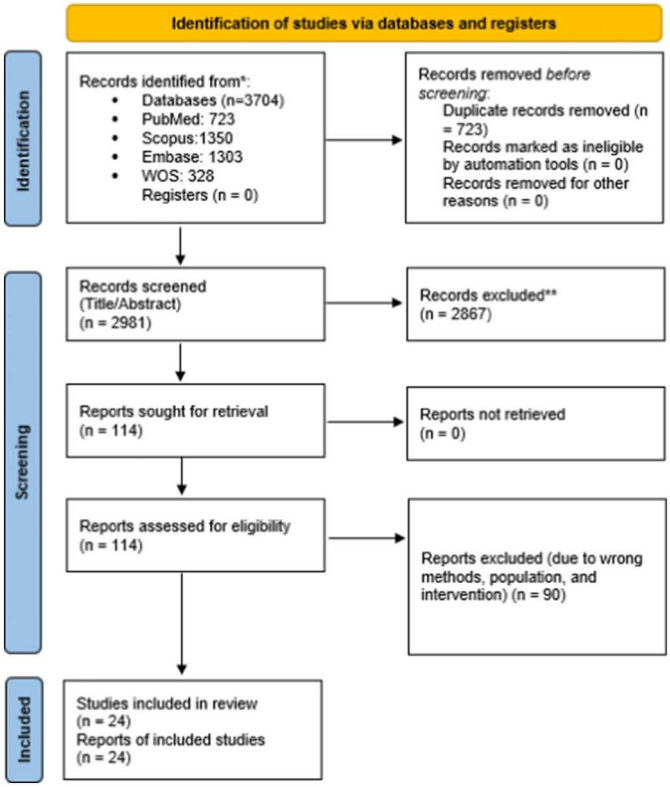

Fig. 1. PRISMA flow diagram of included studies.

Table 1
Descriptive outcomes of included systematic review articles.

Study	Country	Number of pregnancies/patients	Type of valve replacement	Anticoagulation regimen during pregnancy				Fetal and neonatal complications	Maternal mortality and complications	Number of live births
				Week 0–6 (first trimester)	Week 6–12 (first trimester)	Week 12–24 (second trimester)	Week 24–36 (third trimester)			
[17]	Iran	54	39 MVRs,9 AVRs, and 6 DVRs (Aortic and Mitral) (All Mechanical Protheses)	UFH	UFH	Warfarin	Warfarin	• 2 Stillbirths • 3 Neonatal Deaths • 1 Low Birth Weight baby • 1 Warfarin Embryopathy	• 2 Maternal Deaths • 9 Maternal thromboembolic events include 7 Valve Thrombosis • 2 Maternal Hemorrhagic complications	39
[43]	South Korea	8	8 MVRs,1 AVR, and 1 DVR (Aortic and Mitral) (All Mechanical Protheses)	Warfarin + ASA	Warfarin + ASA	Warfarin + ASA	Arfarin + ASA	• 2 Low Birth Weight babies	• 2 Maternal thromboembolic events • 1 Valve Thrombosis	4
		23	15 MVRs,3 AVRs, and 1 DVR (Aortic and Mitral) (All Mechanical Protheses)	Warfarin + ASA	LMWH (Nadroparin) + ASA	Warfarin + ASA	Warfarin + ASA	• 2 Low Birth Weight babies • 2 fetal loss	• 3 Maternal thromboembolic events • 2 Valve Thrombosis	21
[26]	Iran	11	8 MVRs and 3 AVRs (All Mechanical Protheses)	Warfarin	UFH	Warfarin	Warfarin	• 3 Spontaneous Abortions	• 6 Valve Thrombosis	7
[22]	Denmark	23	N/A	Warfarin or phenprocoumon	LMWH or UFH	Warfarin or phenprocoumon	Warfarin or phenprocoumon	• 5 Preterm Labors • 0 Neonatal Death	• 1 Maternal Death • 1 Maternal thromboembolic event 5 Maternal Hemorrhagic complications	N/A
[44]	India	23	N/A	UFH	UFH	Acenocoumarol	Acenocoumarol	• 4 Spontaneous Abortions • 2 Preterm Labor • 5 IUGRs • 1 Stillbirth	• 0 Maternal Death • 1 Maternal thromboembolic event • 4 Maternal Hemorrhagic complications	18
[45]	South Africa	62 pregnancies in 60 women	51 MVRs,2 AVRs, and 9 DVRs(Aortic and Mitral)	UFH	UFH	Warfarin	Warfarin	• 14 Spontaneous Abortions • 9 Stillbirths	N/A	38
[46]	South Africa	61	44 MVRs,1 AVRs, and 11 DVRs(Aortic and Mitral) (59 Mechanical Protheses +2 Bioprosthetic Valves) *Three patients with mechanical prothesis stopped medication of their own.	Heparin	Heparin	Warfarin	Warfarin	• 12 Spontaneous Abortions • 6 Stillbirths • 4 Warfarin Embryopathies • 2 Neonatal Deaths	• 4 Valve Thrombosis • 8 Maternal Hemorrhagic complications	41
[47,48]	Egypt	75	20 DVRs(Aortic and Mitral) *Other valve not mentioned	Warfarin	Warfarin	Warfarin + ASA	Warfarin + ASA	• 6 Spontaneous Abortions • 1 Stillbirths	• 0 Maternal Thromboembolic events • 2 Maternal Hemorrhagic complications	N/A
		25	4 DVRs(Aortic and Mitral) *Other valve not mentioned	Phenindione	Phenindione	Phenindione + ASA	Phenindione + ASA	• 3 Spontaneous Abortions • 1 Stillbirths	• 0 Maternal Thromboembolic events • 0 Maternal Hemorrhagic complications	N/A
[33]	Egypt	17	N/A	Warfarin	Warfarin	N/A	N/A	• 11 Spontaneous Abortions • 0 Embryopathies	• 0 Maternal Deaths • 0 Maternal Thromboembolic events • 0 Valve Thrombosis	4
		28	N/A	Heparin Calcium	Heparin Calcium	N/A	N/A	• 5 Spontaneous Abortions • 0 Embryopathies	• 0 Maternal Deaths • 4 Maternal Thromboembolic events • 4 Valve Thrombosis	16
		53	N/A	LMWH (Enoxaparin Sodium)	LMWH (Enoxaparin Sodium)	N/A	N/A	• 12 Spontaneous Abortions • 0 Embryopathies	• 3 Maternal Deaths • 4 Maternal Thromboembolic events • 4 Valve Thrombosis	31
		2	N/A	UFH	UFH	N/A	N/A	• 1 Spontaneous Abortions • 0 Embryopathies	• 0 Maternal Deaths • 0 Maternal Thromboembolic events • 0 Valve Thrombosis	0
[18]	Turkey	25	N/A	UFH	UFH	Warfarin	Warfarin	• 7 Spontaneous Abortions • 11 Preterm labors • 3 Stillbirths	• 0 Maternal Deaths • 4 Valve Thrombosis	N/A
		12	N/A	ASA	ASA	ASA	ASA	• 0 Spontaneous Abortions • 1 Preterm labor • 0 Stillbirths	• 0 Maternal Deaths • 1 Valve Thrombosis	N/A

(continued on next page)

[27]	Turkey	25	(All Mechanical Protheses)	Warfarin	LMWH	Warfarin	Warfarin	• 3 Spontaneous Abortions • 0 Stillbirths • 1 Therapeutic Abortion	• 3 Maternal thromboembolic events (All were Valve Thrombosis) • 1 Maternal Hemorrhagic complication	N/A
		31	(All Mechanical Protheses)	Warfarin + ASA	Warfarin + ASA	Warfarin + ASA	Warfarin + ASA	• 7 Spontaneous Abortions • 0 Stillbirths • 17 Therapeutic Abortion	• 5 Maternal thromboembolic events (All were Valve Thrombosis) • 5 Maternal Hemorrhagic complication	N/A
[49]	Bangladesh	182	140 MVRs,and 42 AVRs (All Mechanical Protheses)	Heparin	Heparin	Warfarin	Warfarin	• 64 Spontaneous Abortions • 6 Preterm labors • 5 Warfarin Embryopathies	• 1 Maternal Death • 0 Maternal Thromboembolic event • 83 Maternal Hemorrhagic complications	N/A
		83	66 MVRs,and 17 AVRs (All Bioprosthetic Valves)	Heparin	Heparin	Warfarin	Warfarin	• 5 Spontaneous Abortions • 2 Preterm labors • 0 Warfarin Embryopathies	• 0 Maternal Death • 0 Maternal Thromboembolic events • 8 Maternal Hemorrhagic complications	N/A
[20]	Turkey	51	36 MVRs,5 AVRs, and 10 DVRs(Aortic and Mitral) (All Mechanical Protheses)	LMWH	LMWH	Warfarin	Warfarin	• 4 Spontaneous Abortions • 4 Therapeutic Abortions • 8 Preterm Labors • 4 Stillbirths • 12 Low Birth Weight babies	• 1 Maternal Death • 24 Maternal Thromboembolic event include 21 Valve Thrombosis • 12 Maternal Hemorrhagic complications	N/A
		22	13 MVRs,4 AVRs, and 5 DVRs(Aortic and Mitral) (All Mechanical Protheses)	LMWH	LMWH	LMWH	Warfarin	• 1 Spontaneous Abortion • 1 Therapeutic Abortion • 3 Preterm labors • 1 Stillbirth • 4 Low Birth Weight babies	• 0 Maternal Death • 9 Maternal Thromboembolic event include 8 Valve Thrombosis • 3 Maternal Hemorrhagic complications	N/A
[50]	Iran	16 pregnancies in 16 women	12 MVRs,3 AVRs, and 1 DVR (Aortic and Mitral)	LMWH	LMWH	N/A	N/A	• 0 Preterm labors	• 0 Maternal Deaths • 0 Maternal Thromboembolic events • 2 Maternal Hemorrhagic complications	15
		15 pregnancies in 15 women	13 MVRs,1 AVR, and 1 DVR (Aortic and Mitral)	UFH	UFH	Warfarin	UFH	• 2 Preterm labors	• 0 Maternal Deaths • 3 Maternal Thromboembolic events • 6 Maternal Hemorrhagic complications	12
[19]	Egypt	30	16 MVRs,4 AVRs, and 10 DVRs(Aortic and Mitral)	LMWH	LMWH	Warfarin	Warfarin	• 0 Preterm labors • 0 Warfarin Embryopathies • 1 Stillbirth	• 4 Maternal Hemorrhagic complications	N/A
[15]	China	13	8 MVRs,1 AVR, and 4 DVRs (Aortic and Mitral)	LMWH	LMWH	Warfarin	Warfarin	• 0 Preterm labors • 1 Warfarin Embryopathy • 0 Low Birth Weight babies	• 0 Maternal Thromboembolic events • 1 Maternal Hemorrhagic complication	10
[51]	Pakistan	75	45 MVRs,19 AVRs, and 11 DVRs(Aortic and Mitral)	Warfarin	Warfarin	Warfarin + ASA	Warfarin + ASA	• 21 Spontaneous Abortions • 15 Preterm labors • 19 Low Birth Weight babies	N/A	N/A
[24]	Poland	15 pregnancies in 12 women	6 MVRss, 8 AVRs, and 1 TVR	N/A	LMWH or UFH	Warfarin	Warfarin	• 0 Spontaneous Abortions	• 0 Maternal Deaths • 6 Maternal Thromboembolic events • 6 Maternal Hemorrhagic complications • 6 Valve Thrombosis	N/A
[25]	Saudi Arabia	164 pregnancies in 35 women	N/A	N/A	LMWH	Warfarin	Warfarin	• 1 Spontaneous Abortion • 3 Stillbirths	• 2 Maternal Thromboembolic events • 2 maternal hemorrhagic complications	141
		148 pregnancies in 28 women	N/A	N/A	UFH	Warfarin	Warfarin	• 0 Spontaneous Abortions • 1 Stillbirth	• 1 Maternal Thromboembolic events • 1 Maternal Hemorrhagic complication	138
[28]	Israel/USA	30	Mechanical valve prosthetic valve (MPHV)	LMWH	LMWH	LMWH	LMWH		• 2 Maternal hemorrhagic complication • 9 antenatal bleeding	N/A

[21]	Turkey	100 pregnancies in 68 patients	N/A	Warfarin	Warfarin	Warfarin	Warfarin	• 19 Abortions • 3 Still birth • 5 Neonatal deaths • 5 Fatal malformations	• 3 Maternal deaths • 4 Thromboembolic events • 9 Arterial fibrillations • 6 Cardiac failures • 2 Antenatal bleeding • 3 Hematoma formation • 3 Transfusion	68
		18 pregnancies in 16 patients	N/A	UFH	UFH	UFH	UFH	• 2 Abortions • 0 Still birth • 2 Neonatal death • 0 Fatal malformation	• 2 Maternal deaths • 2 Thromboembolic events • 2 Arterial fibrillations • 2 Cardiac failure • 1 Antenatal bleeding • 4 Hematoma formation • 5 Transfusions	14
			18 pregnancies in 17 patients	N/A	No anticoagulation	No anticoagulation	No anticoagulation	No anticoagulation	• 3 Abortions • 0 Still birth • 1 Neonatal death • 0 Fatal malformation	• 0 Maternal death • 0 Thromboembolic events • 1 Arterial fibrillation • 2 Cardiac failures • 0 Hematoma formation • 1 Transfusion 14
[16]	Italy	71 pregnancies in 52 patients	35 MVRs, 11 AVRs, 11 DVRs (Aortic and Mitral)	Warfarin	Warfarin	Warfarin	Warfarin	• 23 Abortions • 5 Still Births • 2 Embryopathies	• 0 Maternal death • 0 Hemorrhagic complication • 0 Thromboembolic events	41
[29]	England	19 pregnancies of 15 women		LMWH	LMWH	LMWH	LMWH		• 1 Maternal death • 3 Thrombotic complications	N/A
[23]	Egypt	20 pregnancies and women	12 MVRs, 5 AVRs, 3 DVRs	UFH	UFH	UFH	UFH	• 3 Abortions	• 0 Maternal death • 2 Antepartum bleeding • 0 Thrombotic complications	17
		20 pregnancies and women	14 MVRs, 4 AVRs, 2 DVRs	LMWH	LMWH	LMWH	LMWH	• 5 Abortions	• 0 Maternal death • 2 Antepartum bleeding • 1 Thrombotic complications	14

Abbreviations: MVR, mitral valve replacement; AVR, aortic valve replacement; TVR, tricuspid valve replacement; DVR, double valve replacement; LMWH, low molecular weight heparin; Subq, subcutaneous; UFH, unfractionated heparin; ASA, acetylsalicylic acid (aspirin); IUGR, intrauterine growth restriction.

Risk of bias and publication bias assessment

We used the Quality Assessment tool (QUADS-2) to evaluate the risk of bias and clinical applicability of the studies by MG and AB [12]. The bias evaluation was divided into four components: Patient Selection, Index Test, Reference Standard, and Flow and Timing. The clinical applicability of the initial three sections was evaluated and the contentious aspect was deliberated with the third researcher (MF) to achieve consensus (Online Table 4). We used funnel plot analysis along with statistical techniques (The Begg's test and Egger regression test) to evaluate publication bias.

Data analysis

For data analysis, we utilized Stata 14 software (StataCorp LP, College Station, TX, USA). The results were presented as mean/SD with a 95 % confidence interval and visualized in a forest plot. We utilized the I2 statistic [13] to assess heterogeneity among eligible studies and the random effects model provided significant heterogeneity. Finally, to explore the possibility of publication bias, we used eye assessment of Egger's regression analysis and funnel plot symmetry [14].

Result

Study selection

The current review was completed using the PRISMA checklist. An initial comprehensive search from the inception to January 2024, conducted in PubMed, Scopus, Embase, and WOS, led to 3704 results, of which 723 records were duplicates (Fig. 1). After screening the titles and abstracts of 2981 selected studies, 2867 additional papers were discarded being review articles, irrelevant studies, or articles written in a language other than English. The remaining 114 articles were assessed for the eligibility through their full-text which resulted in exclusion of 90 articles due to wrong methods, population, intervention, and irrelevant findings. Finally, in this systematic review, 24 papers were selected (Table 1), of which 15 quantitative studies were qualified for meta-analysis (Online Table 5). This meta-analysis included 1255 pregnancies in total.

Fetal complications (FC)

Embryopathies

Only one article [15] evaluated embryopathies in the LMWH or UFH group; hence, this subgroup's analysis is not valuable and reliable. The analysis results for the warfarin subgroup were a prevalence of 1 % (95 % CI: −0.00-0.03; $I^2 = 56.2$ %) in 5 studies [15–19] (Fig. 2).

Low birth weight babies (LBWs)

There were not enough articles on this complication to investigate again in the LMWH or UFH subgroup. But in the warfarin group, the prevalence of LBWs was 3 % (95 %CI:0.01–0.05; $I^2 = 3.2$ %) in 3 studies [15,17,20] (Fig. 3).

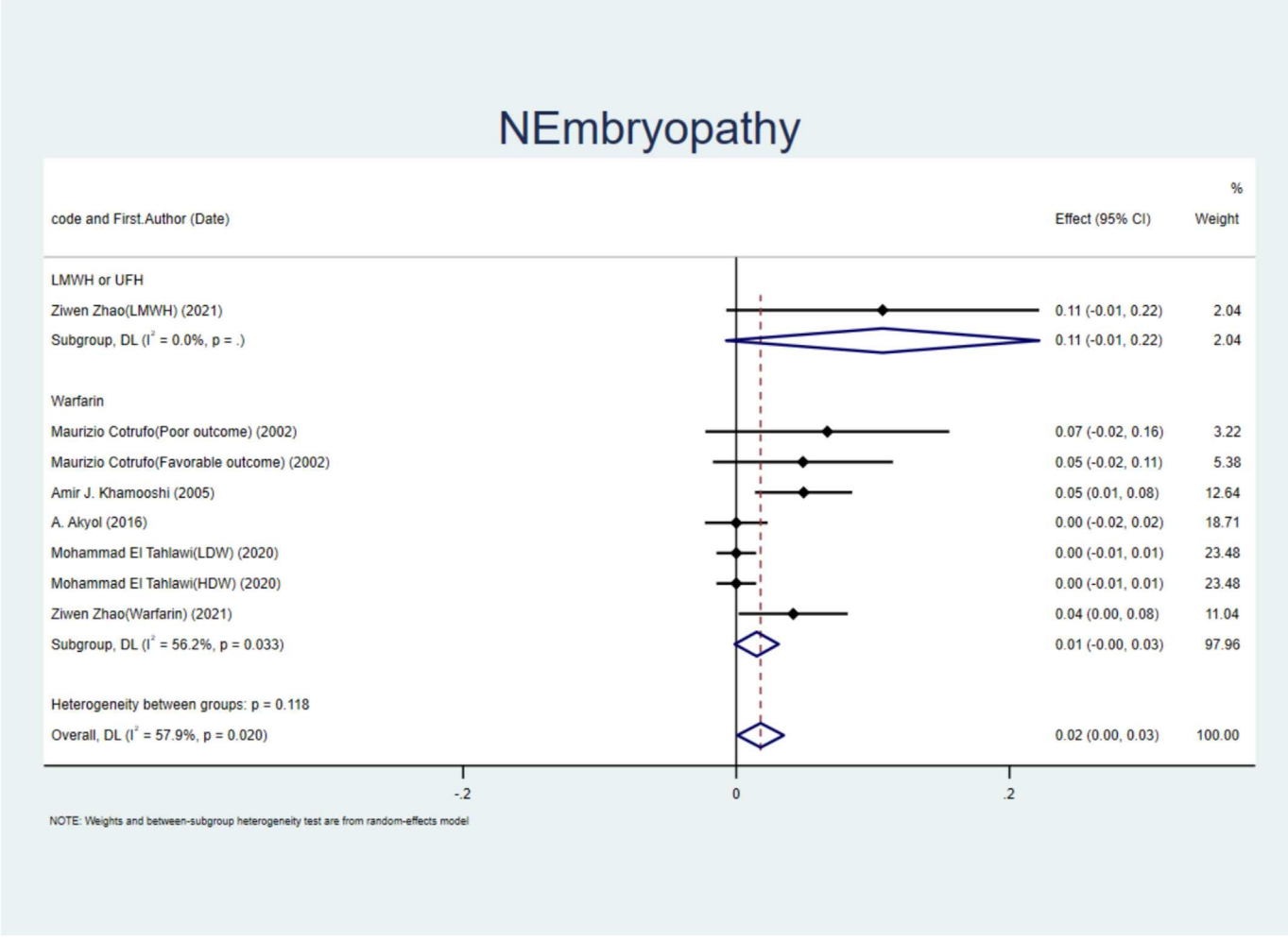

Fig. 2. Forest plot of the prevalence of emberyopathy. The weight of each paper on the meta-analysis is indicated by each parallelogram, the 95 % CI is visualized by the interval within the boundaries. Literature is presented based on random effect model.

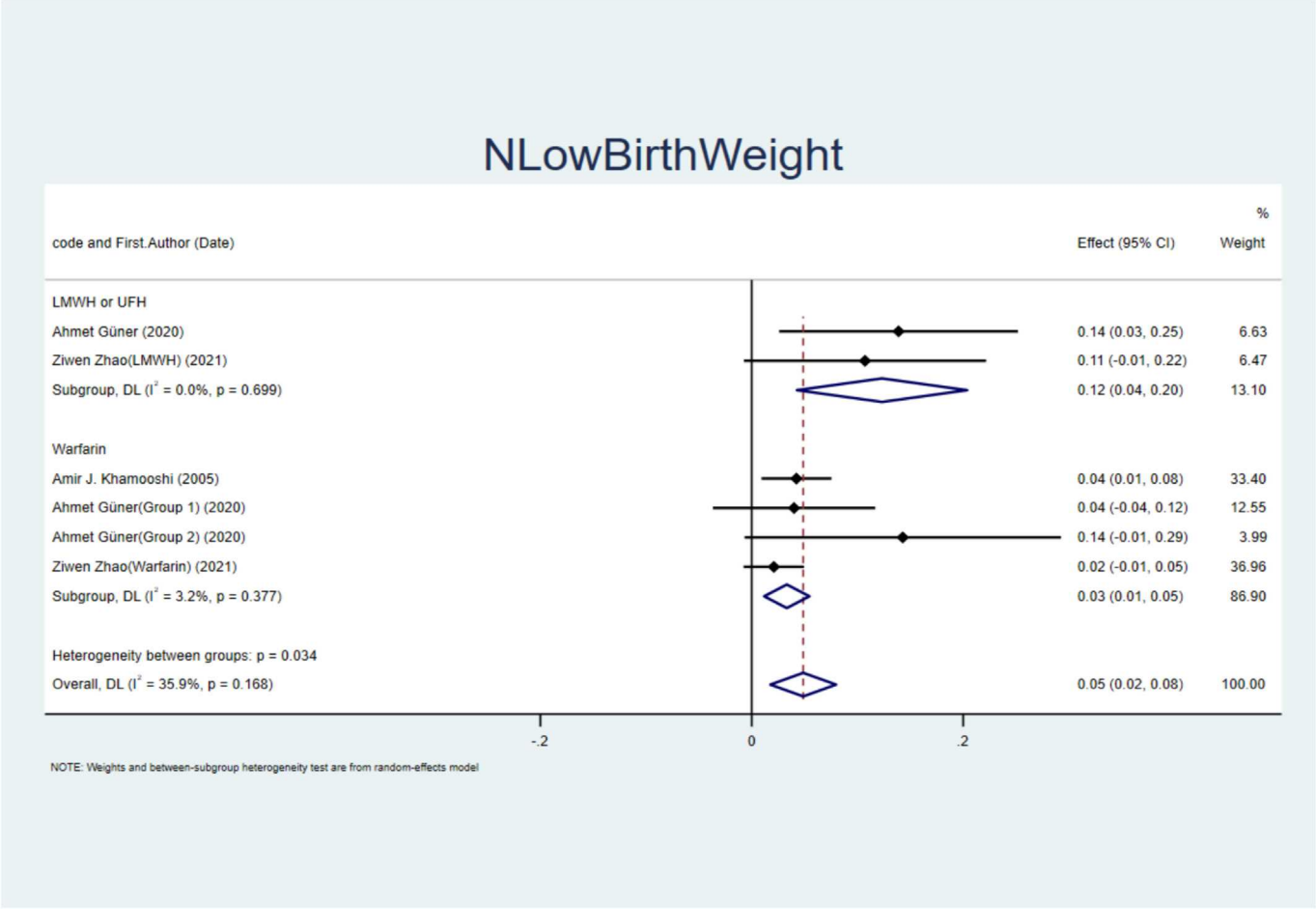

Fig. 3. Forest plot of the prevalence of low-birth-weight infants. The weight of each paper on the meta-analysis is indicated by each parallelogram, the 95 % CI is visualized by the interval within the boundaries. Literature is presented based on random effect model.

Neonatal death

In this category, the data about LMWH or UFH subgroups was reported in only one article, but in the warfarin subgroup, the prevalence was 3 % (95 %CI:-0.00–0.06; $I^2 = 41.8$ %) in a total of 3 articles [17,21,22] (Fig. 4).

Preterm labor

The prevalence of preterm labor in the LMWH or UFH subgroup was 9 % (95 %CI:0.04–0.14; $I^2 = 0.0$ %) in 5 studies [15,20–23], and the prevalence in the warfarin subgroup was 8 % (95 %CI:0.03–0.13; $I^2 = 84.1$ %) in a total of 6 studies [15,18–22] (Fig. 5).

Spontaneous abortion

The prevalence of spontaneous abortions in the LMWH or UFH subgroup was 8 % (95 %CI:0.01–0.14; $I^2 = 64.1$ %) in a total of 5 studies [20,21,23–25], and 23 %(95 %CI:0.10–0.35; $I^2 = 90.1$ %) in warfarin group with a total of 7 studies [16–18,20,21,24,26] (Fig. 6).

Stillbirth

The prevalence of stillbirths was 1 %(95 %CI:-0.01–0.04; $I^2 = 59.7$ %) in a total of 4 studies [20,21,25,27] and 0.01 %(95 %CI:-0.00–0.03; $I^2 = 58.0$ %)in a total of 6 studies [16–21] (Online Fig. 1).

Maternal complications (MCs)

Maternal hemorrhagic complications

The prevalence of maternal hemorrhagic complications in the LMWH or UFH subgroup was 18 % (95 %CI:0.09–0.27; $I^2 = 90.7$ %) in a total of 10 studies [15,20–25,27–29], 2 % (95 %CI:0–3; $I^2 = 69.1$ %) in the Warfarin subgroup with a total of 8 studies [15–17,19–22,24], and 2 % (95 %CI:-0.03–0.06; $I^2 = 0.0$ %) in the no anticoagulation regimen subgroup in 3 studies [21,22,27] (Online Fig. 2).

Maternal thromboembolic events

The prevalence of maternal thromboembolic events in the LMWH or UFH subgroup was 3 % (95 %CI:0.00–0.06; $I^2 = 82.4$ %) in a total of 9 studies [15,20–25,27,28], 1 % (95 %CI:0.00–0.03; $I^2 = 56.1$ %) in the Warfarin subgroup with a total of 7 studies [15–17,20–22,24] and 7 % (95 %CI:−0.06–0.19; $I^2 = 84.9$ %)in the no anticoagulation regimen subgroup in 3 studies [21,22,27] (Online Fig. 3).

Valve thrombosis

The prevalence of valve thrombosis in the LMWH or UFH subgroup was 28 % (95 %CI:-0.15–0.71; $I^2 = 94.6$ %) in a total of 3 studies [20,24,27] and 1 % (95 %CI:-0.00–0.03; $I^2 = 55.6$ %) in the Warfarin subgroup, with a total of 6 [16–18,20,24,26] studies (Online Fig. 4).

Live birth

The prevalence of Live births in the LMWH or UFH subgroup was 79 % (95 %CI:0.69–0.88; $I^2 = 55.6$ %)in a total of 3 studies [15,23,25], and in the Warfarin subgroup, it was 41 % (95 %CI:0.27–0.54; $I^2 = 79.8$ %) in a total of 3 studies [15,17,26] (Online Fig. 5).

Cesarean section and NVD

For the Warfarin subgroup, there were not enough articles on the subject, but for the LMWH or UFH subgroup, the prevalence of cesarean

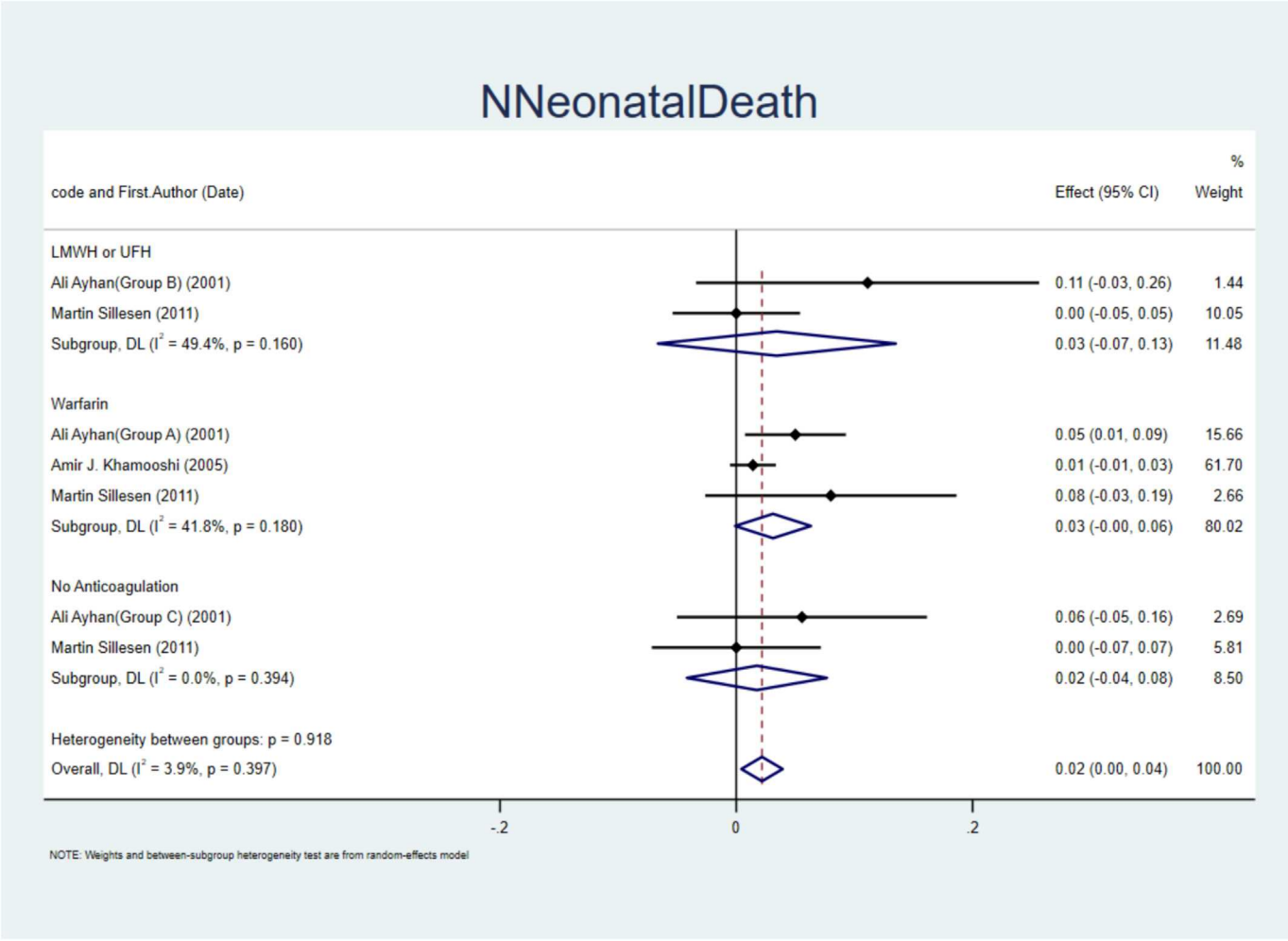

Fig. 4. Forest plot of the prevalence of neonatal death. The weight of each paper on the meta-analysis is indicated by each parallelogram, the 95 % CI is visualized by the interval within the boundaries. Literature is presented based on random effect model.

section was 34 % (95 %CI: 0.23–0.46; $I^2 = 0.0$ %)in 3 studies [23,24,29] and the prevalence of NVD was 36 (95 %CI:0.07–0.65; $I^2 = 88.5$ %) in the LMWH or UFH subgroup in 3 studies [23,24,29] (Online Figs. 6 and 7).

Total abortion

The prevalence of total abortions in the LMWH or UFH subgroup was 15 % (95 %CI:0.09–0.21; $I^2 = 30.1$ %) in a total of 4 studies [20,23–25] and the prevalence in the Warfarin subgroup was 27 % (95 %CI:0.09–0.44; $I^2 = 95.8$ %) in a total of 6 studies [17–20,24,26] (Online Fig. 8).

Publication bias

Egger's test in our meta-analysis ($p = 0.108$) and Begg's funnel plot ($p = 0.002$) indicate no publication bias in the selected articles. Thus, it is clear that reports with both unfavorable and positive outcomes have been published (Online Figs. 9 and 10).

Descriptive results

In the systematic review section of our investigation, 24 articles met our inclusion criteria. The Systematic Review section included 1272 pregnancies in total. We divide the reported data of included studies into four different groups based on the duration of the pregnancy to assess them more efficiently: Week 0–6; week6–12; week12–24 and week 24–36. Maternal and fetal outcomes varied significantly across different therapies. Unfractionated Heparin (UFH) was associated with notable maternal complications and variable fetal outcomes depending on monitoring quality. Low-Molecular-Weight Heparin (LMWH) showed fewer thrombotic and hemorrhagic events, though results were inconsistent across studies, emphasizing the importance of anti-Xa monitoring. Mixed or sequential regimens, such as UFH or LMWH during early pregnancy followed by warfarin, were associated with improved fetal outcomes but presented increased maternal thrombotic risks. Several studies supported low-dose warfarin (≤5 mg/day) as a potentially safer compromise when closely monitored. A complete breakdown of study-level descriptive results is provided in the Online Table 6.

Discussion

This systematic review and meta-analysis aimed to assess pregnancy outcomes in women with mechanical or bioprosthetic heart Valves undergoing anticoagulant therapy with low-molecular-weight heparin (LMWH) or warfarin during pregnancy. Our review synthesized data from 24 studies, with 15 of them contributing to the meta-analysis, representing a total of 1255 pregnancies. Bioprosthetic Heart Valves (BHVs) were associated with significantly fewer pregnancy-related complications compared to mechanical heart valves (MCHVs), likely due to the lower thrombogenicity of BHVs. Patients with BHVs require less intensive anticoagulation therapy, which reduces the risk of hemorrhagic complications and leads to better maternal and fetal outcomes

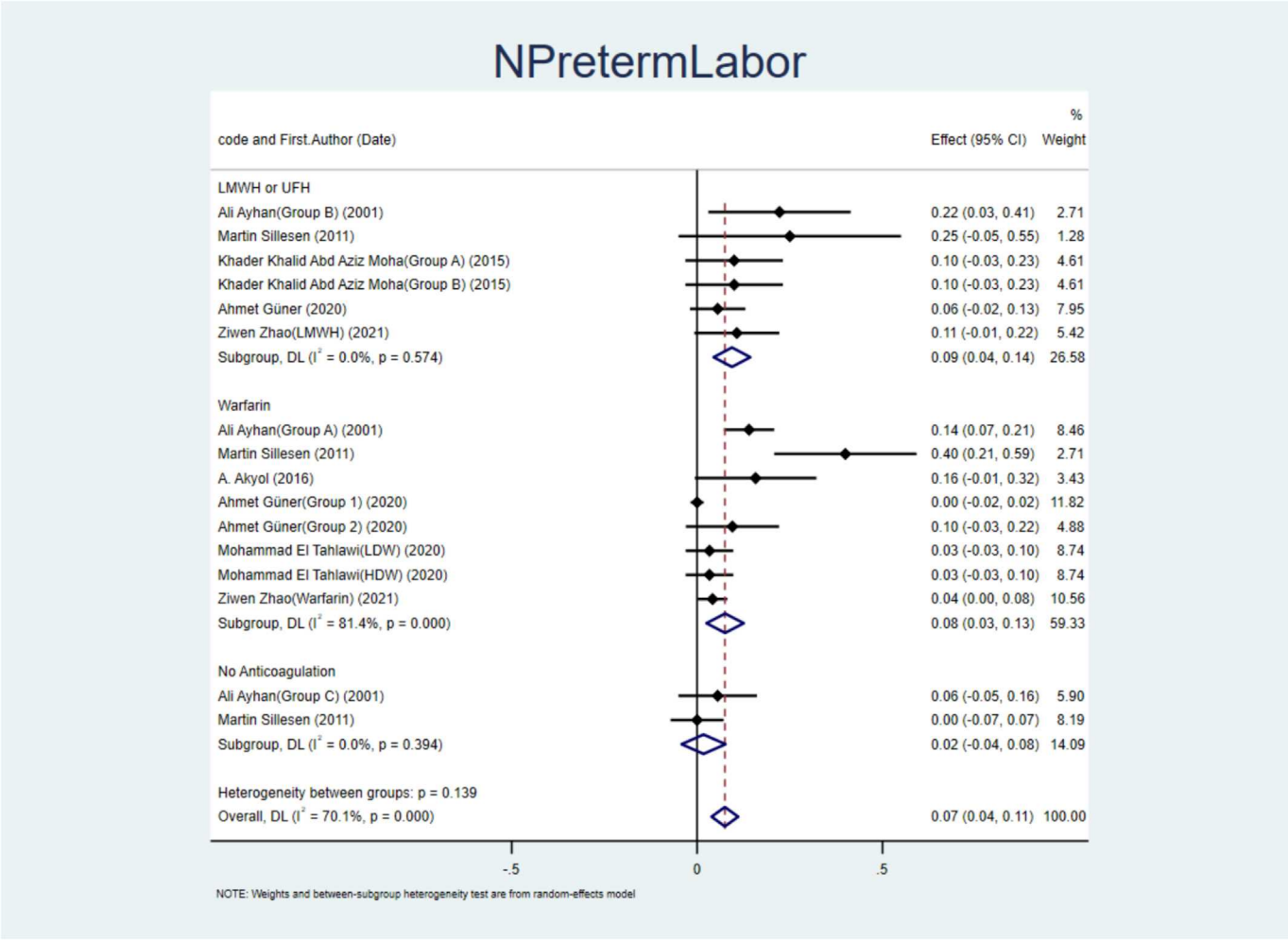

Fig. 5. Forest plot of the prevalence of preterm labor. The weight of each paper on the meta-analysis is indicated by each parallelogram, the 95 % CI is visualized by the interval within the boundaries. Literature is presented based on random effect model.

[30]. Moreover, women with BHVs had better perinatal outcomes and fewer instances of valve thrombosis and heart failure, supporting the use of BHVs in high-risk pregnancies [31,32]. In contrast, Mechanical Heart Valves (MCHVs) require lifelong anticoagulation, which poses substantial risks for both the mother and fetus during pregnancy. MCHVs are hyperthrombogenic and require intensive anticoagulation, resulting in higher rates of thromboembolic complications, valve thrombosis, and maternal morbidity [33]. Although anticoagulation is critical for preventing thromboembolic events, it is associated with severe risks for maternal health, including hemorrhagic complications and pregnancy loss. Careful management and close monitoring of anticoagulation therapy are vital for improving pregnancy outcomes in this group [34].

Anticoagulation therapy reduces the risk of thromboembolic events in pregnant women with MCHVs [35]. This finding is consistent with previous studies highlighting the importance of anticoagulation in preventing valve thrombosis and systemic embolization, which can lead to severe FCs and MCs, including stroke, myocardial infarction, and death. However, it can also cause severe bleeding if not appropriately administered [35]. Clinicians should weigh the benefits of thromboembolic event prevention against the potential risks of bleeding complications when determining the optimal anticoagulation regimen for each patient. We showed that the prevalence of low-birth-weight babies, embryopathies, and neonatal death was higher in the Warfarin subgroup than in the LMWH or UFH subgroup. Because there were not enough articles to analyze these complications in the LMWH or UFH subgroup, the reliability of these findings is limited. The prevalence of spontaneous abortions, preterm labor, and stillbirths was similar between the two subgroups (Table 2).

We also observed that the choice of anticoagulant plays a crucial role in determining the balance between preventing thromboembolic events and bleeding risks. While VKAs have been the mainstay of anticoagulation therapy for MCHV patients, their use during pregnancy can increase the risk of FC, including fetal demise and characteristic embryopathies [36]. In contrast, LMWH and UFH are safer for the fetus but may be less effective in preventing thromboembolic events in this population or even have a higher risk of thrombosis [37,38]. LMWH, on the other hand, has more predictable pharmacokinetics, is easier to administer, and causes fewer complications such as thrombocytopenia and osteoporosis compared to UFH [39]. It is particularly beneficial for managing high-risk pregnancies, as it significantly reduces the incidence of adverse maternal outcomes, such as preeclampsia and fetal growth restriction [40]. Additionally, studies indicate that LMWH is associated with better fetal outcomes, including higher live birth rates (92 %) when compared to other anticoagulation regimens, such as warfarin or sequential therapies [8]. These findings make LMWH the preferred anticoagulant for most pregnant women with mechanical heart valves.

In the included studies, the prevalence of live births was higher in the LMWH or UFH regimen. The prevalence of cesarean section and NVD was similar in the LMWH or UFH regimen subgroup, while there were not enough articles to analyze the Warfarin subgroup. The prevalence of total abortions was higher in the Warfarin subgroup, while the

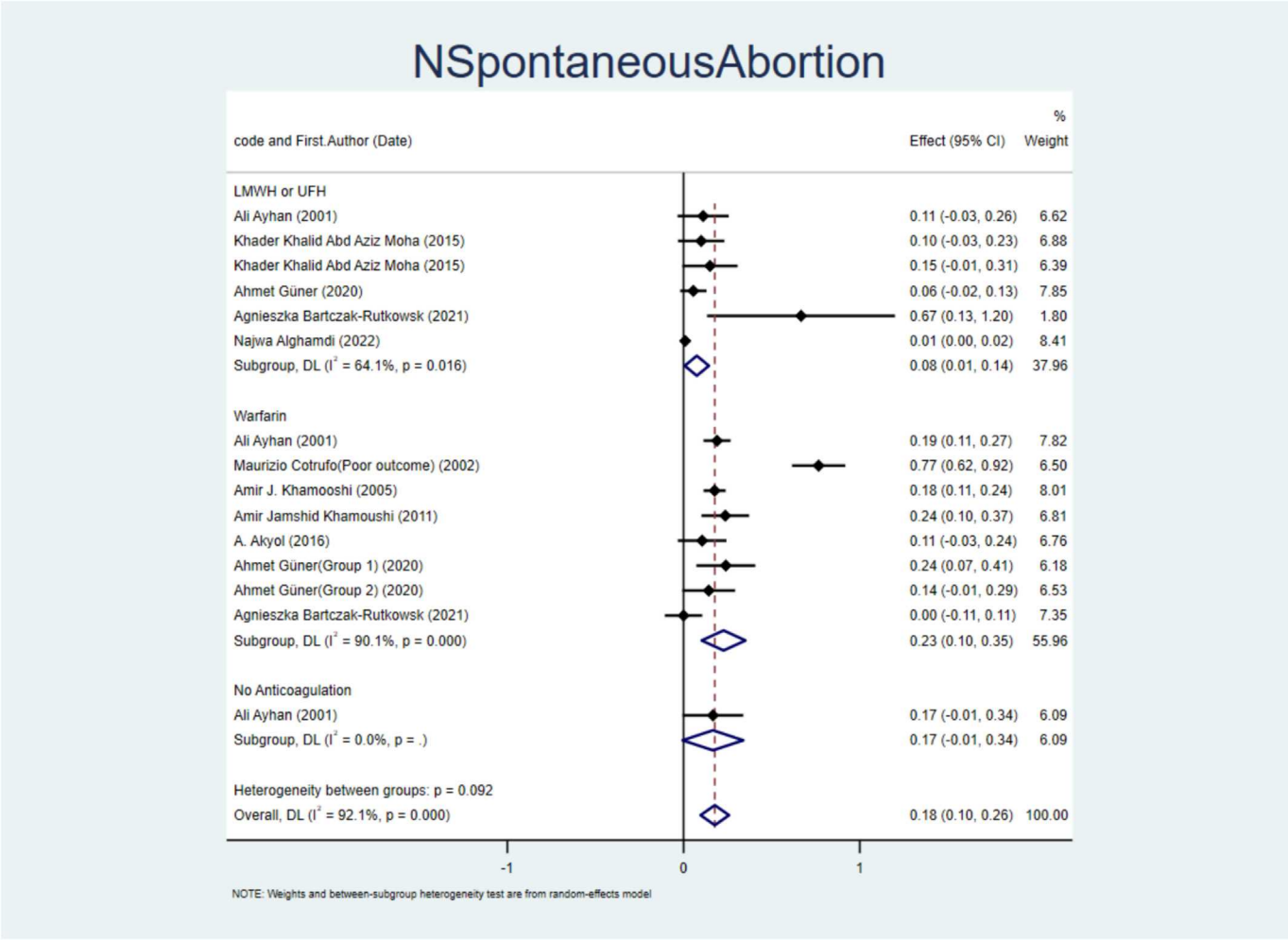

Fig. 6. Forest plot of the prevalence of spontaneous abortion. The weight of each paper on the meta-analysis is indicated by each parallelogram, the 95 % CI is visualized by the interval within the boundaries. Literature is presented based on random effect model.

prevalence of therapeutic abortions was only available for the LMWH or UFH subgroup. In general, UFH is used primarily during early pregnancy as it does not cross the placenta, reducing fetal risks. However, its use is associated with increased maternal complications, such as hemorrhage and valve thrombosis [41]. While UFH has been effective in preventing fetal complications in some cases, its high variability and the need for strict monitoring complicate its use [23]. Studies have shown that UFH therapy, especially in women with mechanical heart valves, requires frequent adjustments to maintain therapeutic levels, which can be difficult during pregnancy [42]. Additionally, UFH regimens have been associated with a higher rate of maternal morbidity and complications [41]. The comparison between LMWH and Warfarin further highlights the complexities of anticoagulation therapy during pregnancy. Warfarin, although effective in preventing thromboembolic events, poses significant risks for fetal complications, including embryopathy and fetal death, especially at higher doses [36]. Conversely, LMWH is safer for the fetus and offers a more favorable safety profile, but may be less effective in preventing thromboembolic events in women with mechanical heart valves, especially if not adequately monitored [37,38].

Overall, regarding the sequential anticoagulation regimens involving UFH, LMWH, and Warfarin, studies have shown that early switching from warfarin to heparin during the first trimester of pregnancy can significantly reduce fetal wastage and improve maternal outcomes [47]. However, delaying the transition increases thrombosis risk, emphasizing the importance of early intervention to balance maternal and fetal risks [10]. Sequential therapy may provide a safer alternative to full-course anticoagulation, though challenges remain in optimizing its outcomes for both the mother and the fetus.

Limitations

This meta-analysis faced limitations, including underpowered subgroup analyses (notably for fetal outcomes with LMWH/UFH), methodological heterogeneity across studies, and a lack of sensitivity analyses due to limited data on stillbirths and embryopathies. Sequential anticoagulation strategies were not evaluated separately, hindering risk comparison. Potential publication bias and selective reporting remain concerns, despite no significant statistical evidence. Lastly, the study did not assess long-term maternal or neonatal outcomes, highlighting the need for future prospective and longitudinal research.

Conclusion

Antithrombotic agents, including Warfarin, LMWH, and UFH, are widely used in pregnant patients with mechanical or bioprosthetic valves. Maternal hemorrhagic complications were more prevalent in patients taking LMWH or UFH compared to those on Warfarin or not receiving anticoagulation therapy. Nonetheless, in the LMWH or UFH group, the live birth rate was significantly higher than the Warfarin group. Due to the methodological and clinical heterogeneity among the included studies, findings should be interpreted with caution,

Table 2
Summary of meta-analysis results. LMWH: Low-Molecular-Weight Heparin, UFH: Unfractionated Heparin, CI: Confidence Interval, NVD: Normal Vaginal Delivery.

	Groups	Number of studies	Prevalence (%)	95 % CI	I^2(%)	Within group *p*-value	Between group *p*-value
Maternal mortality and complications							
Maternal hemorrhagic complications	Warfarin	11	2	(0–3)	69.1	0.000	0.002*
	LMWH or UFH	11	18	(0.09–0.27)	90.7	0.000	
	No Anticoagulation	3	2	(−0.03–0.06)	0.0	0.396	
Maternal thromboembolic events	Warfarin	9	1	(0.00–0.03)	56.1	0.020	0.476
	LMWH or UFH	10	3	(0.00–0.06)	82.4	0.000	
	No Anticoagulation	3	7	(−0.06–0.19)	84.9	0.001	
Valve thrombosis	Warfarin	8	1	(−0.00–0.03)	55.6	0.027	0.430
	LMWH or UFH	3	28	(−0.15–0.71)	94.6	0.000	
	No Anticoagulation						
Fetal and neonatal complications							
Stillbirth	Warfarin	8	1	(−0.00–0.03)	58.0	0.020	0.853
	LMWH or UFH	4	1	(−0.01–0.04)	59.7	0.059	
	No Anticoagulation						
Spontaneous abortion	Warfarin	8	23	(0.10–0.35)	90.1	0.000	0.092
	LMWH or UFH	6	8	(0.01–0.14)	64.1	0.016	
	No Anticoagulation						
Preterm labor	Warfarin	8	8	(0.03–0.13)	84.1	0.000	0.139
	LMWH or UFH	6	9	(0.04–0.14)	0.0	0.574	
	No Anticoagulation						
Neonatal death	Warfarin	3	3	(−0.00–0.06)	41.8	0.180	0.918
	LMWH or UFH						
	No Anticoagulation						
Low birth weight	Warfarin	4	3	(0.01–0.05)	3.2	0.377	0.034*
	LMWH or UFH	2	12	(0.04–0.20)	0	0.699	
	No Anticoagulation						
Embryopathy	Warfarin	7	1	(−0.00–0.03)	56.2	0.033	0.118
	LMWH or UFH						
	No Anticoagulation						
Cesarean section	Warfarin						0.249
	LMWH or UFH	4	34	(0.23–0.46)	0.0	0.526	
	No Anticoagulation						
NVD	Warfarin						0.119
	LMWH or UFH	4	36	(0.07–0.65)	88.5	0.000	
	No Anticoagulation						
Therapeutic abortion	Warfarin						0.196
	LMWH or UFH	3	7	(0.02–0.13)	0.0	0.805	
	No Anticoagulation						
Live birth	Warfarin	3	41	(0.27–0.54)	79.8	0.007	0.000*
	LMWH or UFH	4	79	(0.69–0.88)	55.6	0.080	
	No Anticoagulation						
Total abortion	Warfarin	8	27	(0.09–0.44)	95.8	0.000	0.218
	LMWH or UFH	5	15	(0.09–0.21)	30.1	0.221	
	No Anticoagulation						

* Statistical significance at $p < 0.05$.

underscoring the critical need for further research. A comprehensive evaluation of the advantages and disadvantages of each therapeutic approach would enable physicians to make informed treatment decisions based on a thorough risk assessment for both the mother and the fetus.

Funding

This study was conducted without any financial support from public, commercial, or non-profit funding agencies.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgment

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study. The ethic code is: IR.SBMU.RETECH.REC.1403.831. (Grant Number: 43009152).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2025.08.002.

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