

Evaluation of CHA₂DS₂-VASc risk stratification tool in pregnant women with atrial fibrillation or atrial flutter

Khadeeja Ashai¹, Delia LoSapio², Shayna N. Conner³, Alison G. Cahill⁴, Kathryn J. Lindley^{5*}

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BACKGROUND: The CHA₂DS₂-VASc score has not been validated as a risk stratification tool to determine need for anticoagulation therapy in pregnant women with atrial fibrillation (AF) and atrial flutter (AFL).

HYPOTHESIS: The CHA₂DS₂-VASc score will underestimate thromboembolic event (TE) risk in the hypercoagulable setting of pregnancy.

METHODS: This is a retrospective cohort study of women with pre-existing or newly diagnosed AF or AFL delivering at a tertiary care institution from 2004-2017. AF or AFL was confirmed by electrocardiogram, holter monitor or electrophysiology study. The primary outcome was systemic TE up to six months post-partum (stroke, transient ischemic event, left atrial appendage [LAA] thrombus, other systemic TE); secondary outcome was bleeding events (post-partum hemorrhage or transfusion requirement).

RESULTS: AF was diagnosed in 42/53 (79%) women; 7/53 (13%) had AFL and 4/53 (8%) had both. Therapeutic anticoagulation was prescribed to 11 (21%) women during pregnancy and 13 (25%) post-partum; aspirin was prescribed to 13 (25%) during pregnancy and 11 (21%) post-partum. TE occurred in 3/53 (5.7%) women; TE occurred in 2/35 (5.7%) of women with CHA₂DS₂-VASc scores of 1 (predicted risk 0.5%), and 1/13 (7.7%) with CHA₂DS₂-VASc scores of 2 (predicted risk 1.0%). There was no increased bleeding risk for women on therapeutic anticoagulation during pregnancy (18% vs. 14%, p=0.7), but there was a trend towards more bleeding in women on therapeutic anticoagulation post-partum (31% vs. 10%, p=.09).

CONCLUSIONS: The CHA₂DS₂-VASc score underestimates the risk of systemic TE events in pregnant women with AF/AFL. Pregnancy is a hypercoagulable state which may increase the risk of TE in women with AF/AFL, even postpartum.

Key Words: Atrial fibrillation; Pregnancy; Thromboembolism; Risk stratification; Stroke

INTRODUCTION

Atrial fibrillation is the most commonly reported arrhythmia in pregnancy [1], with a 111% increase noted between 2000 and 2012 [2]. The CHA₂DS₂-VASc classification, commonly used to assess the benefit of anticoagulation, has not been validated in pregnancy, a hypercoagulable state [3-5]. Thromboembolic risk and optimal management of anticoagulation in this population is unknown [6,7]. We sought to analyze the risk of thromboembolic complications in pregnant and postpartum women with atrial fibrillation (AF) and atrial flutter (AFL), and compare these rates to those predicted by the CHA₂DS₂-VASc risk assessment tool.

RESEARCH METHODOLOGY

This is a retrospective cohort study performed at Barnes Jewish Hospital from 2004 to 2017. Fifty-three pregnant women with AF/AFL were identified by chart review, AF or AFL was confirmed by electrocardiogram, Holter monitor or electrophysiology study. Patients were included if they delivered beyond 20 weeks gestation between 2004 and 2017 and had a prior history of or developed de novo AF/AFL up to six months post-partum. Patient thromboembolic risk was estimated using the CHA₂DS₂-VASc scoring system. We also collected information about patient demographics, obstetric and medical history, cardiac medications up to six months post-partum, thromboembolic complications, and maternal and fetal outcomes. The primary outcome was systemic thromboembolic events (TE) up to six months post-partum (stroke, transient ischemic event, left atrial appendage [LAA] thrombus, other systemic TE); secondary outcome was bleeding events (post-partum hemorrhage or transfusion requirement). We used the student's t-test to calculate the probability distribution and Fisher's exact test to determine the statistical significance. The mean age of the studied population was 29.3 years with a relatively

equal distribution of white and African American females at 51% vs. 47% (Table 1). The predominant pre-existing medical condition was hypertension with a prevalence of 14/53 (26%).

TABLE 1
Baseline demographics

Demographic Variables	Number (%) (n=53)
Age (mean, SD)	29.3 (6)
Race	
White	27 (51)
African American	25 (47)
Body Mass Index (mean, SD)	34.6 (8)
Tobacco Use	7 (13)
Pre-existing Medical Conditions	
Hypertension	14 (26)
Diabetes	3 (6)
Stroke/TIA	2 (4)
Heart Failure	4 (8)
Myocardial Infarction	1 (2)

¹Department of Medicine, St. Louis University School of Medicine, USA; ²Student Athlete, University of Lynchburg, USA; ³Maternal-Fetal Medicine, Washington University School of Medicine in St. Louis, USA; ⁴Department of Women's Health, University of Texas at Austin, Dell Medical School, USA; ⁵Cardiovascular Division, Washington University School of Medicine in St. Louis, USA

Correspondence: Kathryn J. Lindley, Cardiovascular Division, Washington University School of Medicine in St. Louis, USA, Telephone: 314-362-1291; e-mail Kathryn.lindley@wustl.edu

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RESULTS

AF was diagnosed in 42/53 (79%); AFL was found in 7/53 (13%), and 4/53 (8%) had both arrhythmias (Table 2). Of the women in the study, 33/53 (62%) had lone AF, while the arrhythmia was associated with other conditions including valvular disease, thyroid disorder, infections, cardiomyopathy, or congenital heart disease in the remainder of the cohort.

TABLE 2
Arrhythmia characteristics

Arrhythmia Characteristics	Pre-existing (n=22)	New Diagnosis (n=31)
Arrhythmia Type		
Atrial Fibrillation	13 (59)	29 (94)
Atrial Flutter	7 (32)	0 (0)
Both	2 (9)	2 (7)
Lone AF vs. associated with other disease		
Lone	10 (46)	23 (74)
Cardiomyopathy	0 (0)	1 (5)
Congenital Heart Disease	9 (41)	1 (3)
Valvular Disease	2 (9)	3 (10)
Thyroid Disorder	0 (0)	1 (3)
Infection	0 (0)	3 (10)

Thromboembolic events occurred in 3/53 (5.7%) women, all of whom had clinical evidence of AF during the pregnancy (Table 3). Of these women, 2/35 (5.7%) had CHA₂DS₂-VASc scores of 1 (predicted risk 0.7%), and 1/13 (7.7%) had a CHA₂DS₂-VASc score of 2 (predicted risk 1.9%). Therapeutic anticoagulation was prescribed to 11 (21%) women during pregnancy and 13 (25%) women post-partum; aspirin was prescribed to 13 (25%) of the women during pregnancy and 11 (21%) post-partum. The secondary outcome of bleeding complications was noted in 8/53 (15%) of women with CHA₂DS₂-VASc scores of either 1 or 2, (transfusion in 8/8 women, postpartum hemorrhage in 5 of the 8 women). There was no significant increased risk for bleeding complications for women on therapeutic anticoagulation during pregnancy (18% vs. 14%, p=0.7), but there was a trend towards more bleeding in women on therapeutic anticoagulation post-partum (31% vs. 10%, p=0.09).

TABLE 4
Thromboembolic event characteristics

Patients	TE Timing	TE Type	CHA ₂ DS ₂ -VASc Score	Anticoagulation at time of TE	Details
1	4 months post-partum	Occipital stroke	2	None	Known paroxysmal AF, was in sinus rhythm during pregnancy; was in AF at time of TE
2	12 weeks gestation	Central retinal artery occlusion	1	None	Diagnosed with AF at time of TE
3	4 months post-partum	LAA thrombus seen on TEE	1	Aspirin	Persistent AF during pregnancy

*TEE - Transesophageal Echocardiogram

TABLE 3
Stratification by CHA₂DS₂-VASc Score

CHA ₂ DS ₂ -VASc Score	1 (n=35)	2 (n=13)	3 (n=4)	4 (n=1)
Arrhythmia During Pregnancy	33 (94)	9 (69)	2 (67)	1 (100)
Anticoagulation During Pregnancy	18 (53)	4 (31)	2 (50)	0 (0)
Aspirin	9 (27)	2 (15)	2 (50)	0 (0)
Therapeutic	8 (23)	3 (23)	0 (0)	0 (0)
Anticoagulation Post-partum	18 (53)	4 (31)	1 (25)	0 (0)
Aspirin	7 (21)	3 (23)	1 (25)	0 (0)
Therapeutic	10 (29)	2 (15)	1 (25)	0 (0)
TE	2 (6)	1 (8)	0 (0)	0 (0)
On Aspirin	1 (3)	0 (0)	0 (0)	0 (0)
On No Anticoagulation	1 (3)	1 (8)	0 (0)	0 (0)
Bleeding Complication	6 (17)	2 (15)	0 (0)	0 (0)

Of the women with TE, one was diagnosed with AF at the time of the stroke, one stroke occurred in a woman non-adherent with enoxaparin with a known history of paroxysmal AF, and one patient developed LAA thrombus while on aspirin therapy with persistent AF during her pregnancy (Figure 1 and Table 4).

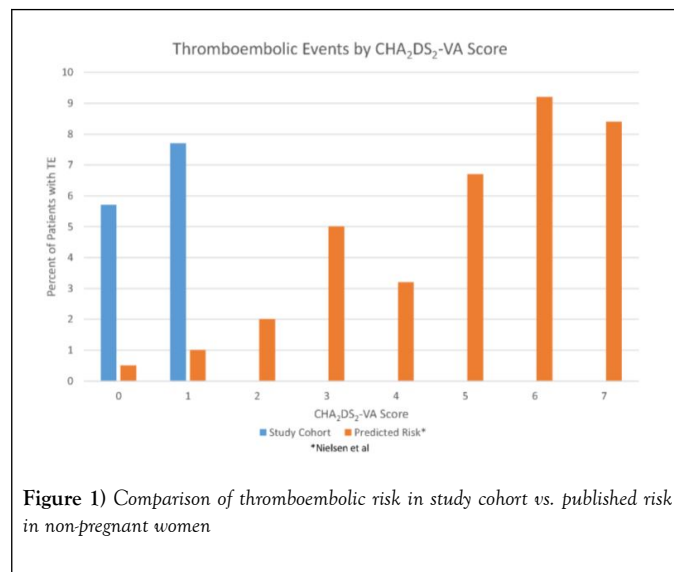


Figure 1) Comparison of thromboembolic risk in study cohort vs. published risk in non-pregnant women

DISCUSSION

This study identified an increased risk of TE in pregnant women with AF/AFL. The risk identified in our study cohort is higher than would be expected based on the calculated CHA₂DS₂-VASc score, the tool commonly applied for the determination of anticoagulation. Additionally, therapeutic anticoagulation was not associated with excessive bleeding risk over the course of the pregnancy, though there was noted to be a trend towards increased post-partum bleeding. All patients had a CHA₂DS₂-VASc of 1 or higher simply by virtue of being female. Current guidelines do not recommend therapeutic anticoagulation for women unless they have two additional risk factors [8]. The predicted risk for a stroke/TIA/other event over our study timeframe is 0.5% for women with no additional risk factors, but the actual event rate was 5.7% in our study population, over 10 times higher [9]. In women with one non-sex risk factor, the predicted risk is 1.0% but was found to be 7.7% in our study population [9].

The currently accepted AHA/ACC/HRS guidelines for management of atrial fibrillation unfortunately do not address anticoagulation in pregnant women [8,10]. Current European Society of Cardiology Guidelines on the management of cardiovascular disease in pregnancy recommend applying the same rules for stroke risk stratification as used in non-pregnant patients [11]. Cumyn et al. surveyed general internists, obstetricians, and cardiologists from 11 countries about their approach to managing anticoagulation of AF in pregnancy. Of 61 respondents, 2/3 based their clinical decision making on the CHADS₂ or CHA₂DS₂-VASc score [7]. The currently accepted risk stratification system of using the CHA₂DS₂-VASc score takes into account female sex as a risk modifier in the assessment of possible thromboembolic events as females are noted to show greater rates of TEs as compared to men, in the presence of additional thromboembolic risk factors [9,12]. In our pregnant population, 66% of patients carry a low risk score, implying a low risk of thromboembolic events. However, our study suggests this may be a significant underestimation of risk in this population, and research on the physiology of pregnancy and hypercoagulability may provide explanations for this discrepancy.

Some of the unique features of pregnancy include increased blood volume and venous stasis [13], increased estrogen and progesterone levels [14], and an increase in pro-coagulants such as fibrinogen/von Wille brand factor and decrease in anti-coagulant factors such as protein S, which can contribute to the higher risk of thromboembolism. Secondly, the risk of adverse events may be higher because pregnancy is itself a potentially arrhythmogenic state [5,15]. The increase in potential arrhythmias occurs in the setting of increased left ventricular mass and increased left atrial size to accommodate the increased blood volume precipitating additional myocardial stretch as well as physiologic tachycardia (up to 10-15 beats per minute higher than normal) which potentiates irregular atrial rhythms [1,14]. Third, women with underlying cardiovascular disease are at higher risk of complications and progression due to the aforementioned physiologic factors, thereby increasing their risk of thromboembolism [16]. Our study had a combination of women with lone AF as well as those with associated conditions. Those with lone AF may have been related to the physiologic changes previously mentioned.

Another important finding from our work is that the circumstances leading up to the observed complications were very diverse. One woman was adherent to the prescribed aspirin therapy after having been in persistent AF during her pregnancy and was noted to have a left atrial appendage thrombus four months postpartum. Another patient was known to have paroxysmal AF but had been non-adherent with her enoxaparin when she developed her occipital stroke four months postpartum. The third patient was pregnant at the time of her central retinal artery occlusion with no prior history of arrhythmia and was thus not on any anticoagulation or anti-platelet therapy. Complications also occurred at different temporal points, both during pregnancy as well as post-partum. The heterogeneity of factors preceding complications suggests that further research is necessary to develop appropriate risk stratification tools.

An additional factor that complicates management of AF/AFL in pregnant women is AF burden, and the relatively brief duration of the hypercoagulable state of pregnancy (nine months of pregnancy + three months post-partum). One study looked at the AF burden over a 14-day

period for patients not on anticoagulation. It found that those with the highest AF burden, noted at >11.4% of the monitored time period, had a 3x higher risk of TE with a median time of 8 months to time of the TE event [17]. This raises the question of the utility of assessing AF burden in the pregnant/postpartum population which we have demonstrated may already be at higher risk of TE complications. Study of AF burden in interaction with CHA₂DS₂-VASc scoring in the setting of cardiovascular implantable electronic devices, allowing for longer continuous monitoring than 14 days, also showed that AF duration increases the annual risk of stroke and systemic emboli, the metric used in this particular study [18].

LIMITATIONS

Our analysis is retrospective and identifies only 53 cases. Larger studies and prospective trials are needed to further inform best practices for anticoagulation use for AF in pregnancy. Additionally, our follow-up was limited to 6 months and two events occurred at 4 months. This short window may underestimate the true incidence of postpartum thromboembolism from AF/AFL. Due to the small sample size, lack of difference in bleeding complications in women on therapeutic anticoagulation could have resulted due to type 2 error.

FURTHER RESEARCH

The higher than anticipated risk of TE events in our study supports the need for further research on optimal anticoagulation strategies for women with AF in pregnancy. This includes prospective, randomized studies on anticoagulation strategies as well as evaluation of pregnancy-specific risk assessment tools.

CONCLUSION

There are no data-driven guidelines regarding management of atrial fibrillation and atrial flutter during pregnancy at present. The CHA₂DS₂-VASc schema is commonly used as a risk assessment tool, but does not account for the hypercoagulable physiology and arrhythmogenic state of pregnancy. This study suggests CHA₂DS₂-VASc may under-estimate thromboembolic risk in this unique population. Given the lack of a validated risk assessment tool and the potentially high morbidity/mortality of thromboembolic events in this young population, further research is necessary to develop evidence-based guidelines for the growing population of pregnant women with a history of AF.

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