International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

The Value of Fetal Doppler Indices as Predictors of Perinatal Outcome in Pregnant Women on Thromboprophylaxis

Eman Zein El Abedein Farid[1], Hamada Ashry Abdel Wahed[1], Dr. Heba Qassim Shamardal[1*], Marwa Yahia Mahmoud[1]

[1]*Department of Obstetrics and Gynecology, Faculty of Medicine – Beni-Suef University*

Abstract

Pregnancy thromboprophylaxis aims to avoid a maternal thromboembolism or to improve obstetric outcomes. The aim of study is to determine whether or not the ratio of Doppler indices in the middle cerebral to the umbilical arteries can reliably predict foetal well-being and newborn outcome in pregnant women receiving thromboprophylaxis between 28 and 34 weeks of gestation. This prospective cohort observational study conducted on 72 patients classified into three groups. Group I: 24 women undergoing thromboprophylaxis by low molecular weight heparin (LMWH), Group II: 24 women undergoing thromboprophylaxis by acetylsalicylic acid (ASA) and Group III: 24 pregnant women not undergoing thromboprophylaxis (control group) at the department of Obstetrics and Gynecology at Beni-Suef University Hospital. Doppler ultrasonography was used to examine second- and third-trimester pregnant women undergoing thromboprophylaxis (LMWH or ASA). There was no statistically significant difference between the studied groups as regard history data, gestational age at delivery, neonatal outcome and maternal complications although post-partum hemorrhage rate was higher in LMWH and ASA groups. There was statistically significant difference between the studied groups as regard peak systolic velocity in the middle cerebral artery (MCA PSV). MCA PSV had sensitivity of 84.62, specificity of 83.33, negative predictive value of 55.6 and positive predictive value of 95.7. The doppler indices ratio of the middle cerebral to the umbilical arteries is useful in predicting foetal well-being and newborn outcome in pregnant women receiving thromboprophylaxis between 28 and 34 weeks of gestation

Keywords: Fetal Doppler Indices, Thromboprophylaxis, MCA PSV, LMWH.

Full length article **Corresponding Author*, e-mail: hebaksh67@gmail.com

1. Introduction

Pregnancy thromboprophylaxis often has one of two main aims: either to avoid a maternal thromboembolism or to improve obstetric outcomes. Several organizations and associations have issued guidelines on this hot subject in an effort to reduce the number of cases of unnecessary thromboprophylaxis in pregnant women due to missed or misinterpreted indicators [1]. Doppler ultrasonography's advantage in assessing hemodynamics has led to a steady increase in the scope of its applications. In many positions of the circulatory system, including the umbilical artery, the fetal middle cerebral artery, and the uterine artery [2]. Umbilical artery examination using Doppler ultrasonography yields important characteristics reflective of placental resistance in particular. By adjusting for these factors, IUGR therapy has been shown to drastically reduce foetal and newborn mortality [3]. Because of the brain-sparing effect defined as centralization, hemodynamics of the foetal middle cerebral artery is crucial for the antenatal monitoring and management of clinical problems like feto-maternal haemorrhages and Rh incompatibility [4]. Furthermore, as a component of the "cerebro-placental ratio" that has been extensively studied, foetal middle cerebral artery hemodynamics are crucial for predicting the poor [5]. Doppler ultrasonography is commonly used in obstetrics and provides a reassuring clinical evaluation, but the parameters measured by this method can vary from user to user due to technical factors like the angle of insonation and the breadth of the samples. Fortunately, standardizing these parameters is a straightforward process. Clinical variables of patients, in addition to ultrasound procedures, might influence these factors. Since many pregnant women resort to thromboprophylaxis on the subjective basis of "bad obstetric history," it is important to study the effects of anticoagulants on foetal and placental hemodynamics [6]. Considering the potential impact of thromboprophylaxis on Doppler values is essential. The goal of this research was to determine whether or not the ratio of Doppler indices in the middle cerebral to the umbilical arteries can reliably predict foetal well-being and newborn outcome in pregnant women receiving thromboprophylaxis between 28 and 34 weeks of gestation.

2. Patients and methods

This prospective cohort observational study conducted on 72 patients classified into three groups:

- **Group I:** 24 women undergoing thromboprophylaxis by low molecular weight heparin (LMWH).
- **Group II:** 24 women undergoing thromboprophylaxis by acetylsalicylic acid (ASA).
- **Group III:** 24 pregnant women not undergoing thromboprophylaxis (control group) at the department of Obstetrics and Gynecology at Beni-Suef University Hospital. Doppler ultrasonography was used to examine second- and third-trimester pregnant women undergoing thromboprophylaxis (LMWH or ASA). Control group women were same ages and weeks of pregnancy.

2.1. Sample size calculation

Power analysis for Anova: G*Power Version 3.1.9.2 (Franz Faul, Kiel, Germany). G-POWER was used to establish an appropriate sample size using a 0.05 alpha error probability, 0.95 power, and a 0.25 effect size. Based on the assumptions, 66 samples are needed. By calculating 10 % drop out, so the least total sample size in 3 groups was 72 patients (24 patients in each group).

2.2. Inclusion Criteria for study group

Pregnant women continuing to use low-molecular-weight heparin (LMWH) at prophylactic dose or low-dose acetylsalicylic acid 75mg (ASA) at second or third trimester, certain LMP (Last menstrual period), regular menstrual pattern before pregnancy, singleton pregnancy, between 28: 34 weeks' gestation and spontaneous pregnancy or pregnancy after assisted reproductive technique.

2.3. Exclusion Criteria for groups

Pregnancies below 18-year-old, multiple pregnancies, known fetal genetic or other anomalies, using thromboprophylaxis due to indications (i.e. deep vein thrombosis or prosthetic heart valve, systemic lupus erythematosus), uncertain gestational age, maternal diabetes mellitus and presence of congenital thrombophilia.

2.4. Ethical Consideration

Study protocol had been submitted for approval by the ethics committee on research involving human subjects of Beni-Suef faculty of Medicine**.** Informed verbal consent had been obtained from parents of each participant sharing in the study. Confidentiality and personal privacy had been respected in all levels of the study.

2.5. Methods

The eligible subjects included in this study were subjected to the following: Full history taking, clinical examination and laboratory investigations.

2.5.1. Ultrasound examination

2D Ultrasound (Mindray N7) was carried out in Gynecology and Obstetrics department in Beni-Suef University Hospital, ultrasonography criteria: Ultrasound biometry of the fetus is now the gold standard for assessing fetal growth. The measurements most commonly used were the biparietal diameter, head circumference, abdominal circumference and femur length:

2.5.2. Doppler ultrasonography

In (UmAD*)* samplings, the sampling was done on the area close to the placental end, and PI, RI and S/D values were recorded. Insonation angle was kept below 10 degrees in middle cerebral artery doppler (MCA) measurements, and peak systolic velocity (MCA PSV) and PI values were recorded.

2.6. Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 *(*Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. The used tests were:

- Chi-square test: For categorical variables, to compare between different groups.
- One-way ANOVA: For normally distributed quantitative variables, to compare between two studied groups

3. Results

Table 1 showed that there was no statistically significant difference between the studied groups as regard history data. Table 2 showed that there was no statistically significant difference between the studied groups as ultrasound biometry. Table 3 showed that there was statistically significant difference between the studied groups as MCA PSV and highly statistically significant difference as regard UtA PI. Table 4 showed that there was no statistically significant difference between the studied groups as regard maternal complications although post-partum Hemorrhage rate was higher in LMWH and ASA groups. Table 5 showed that there was no statistically significant difference between the studied groups as regard neonatal outcome. Table 6 showed that MCA PSV had sensitivity of 84.62, Specificity of 83.33, Negative predictive value of 55.6 and Positive predictive value of 95.7. There was no statistically significant difference between the groups as regard gestational age (GA) at delivery (Figure 1).

4. Discussion

No statistically significant differences were seen in the present investigation with respect to age, place of residence, employment, weight, height, body mass index. Corresponding to our findings, El-Demiry et al. (2020) found no significant differences in gestational age (in weeks), past mode of delivery, and current mode of delivery across the groups they examined [7]. Current findings on gestational age at birth showed no statistically significant difference between the groups. Ten patients with recurrent preeclampsia had a mean gestational age of 34.364.6 (26-40) weeks at the beginning of symptoms, according to research by Riyazi et al., (1998). There were 6 (32.8%) recurrences of preeclampsia in the group of women who were given aspirin for prevention.

The average gestational age when the six patients first had recurrent preeclampsia was 34.064.4 (26-38) weeks. There was no statistically significant difference in birth weight between the two groups [8]. Our most recent ultrasound data showed no statistically significant differences in femur length, biparetal diameter, head size, abdomen circumference, or estimated fetal weight (EFW) across the groups (Kg). Statistically significant differences in MCA PSV were seen across groups in the present investigation. Doppler studies of the umbilical artery improve perinatal outcomes in high-risk pregnancies thought to be at risk of placental insufficiency, as reported in a recent update of the 'routine' use of Doppler ultrasound in high-risk pregnant women by Alfirevic et al., (2017) [9]. However, the value of Doppler velocimetry in the assessment of low-risk populations remains unproven. A study by Khalil et al., (2017) found that aberrant MCA Doppler on its own was only moderately predictive of fetal and neonatal morbidity and mortality [10]. Doppler indices of MCA and UA are markedly aberrant in preeclampsia, according to research published in 2016, however diagnostic statistical analysis reveals that these indices have a high specificity but low sensitivity for diagnosing a poor perinatal outcome. Also, the sensitivity and specificity for predicting an unfavorable perinatal outcome were 9% and 9.7% for the MCA/UA PI ratio cerebro-placental ratio (CPR) and MCA/UA RI ratio, respectively. Low-dose aspirin with LMWH substantially reduced PI in the uterine artery but not in the umbilical artery, as observed by Bar et al., (2001) [11]. These findings may lend credence to the idea that reduced placental development, even in the absence of infarction, is due to diminished blood supply. Although the risk of postpartum hemorrhage was greater in the LMWH and ASA groups, the current investigation demonstrated no statistically significant difference between the groups evaluated with relation to maternal complications. Five women (10%) were reported to have suffered at least one episode of bleeding during pregnancy by Bremme et al., (2021) [12]. Although none of them were considered to be life-threatening. Neither preeclampsia nor ablatio-placentae occurred in any of the patients. One type II antithrombin deficient patient had a muscle vein thrombosis at week 6 of pregnancy (2%).

Table 1: Comparison between the studied cases as regard history data.

	Studied cases						**Test**	**P**
	LMWH group (n=24)		ASA group (n=24)		Control (n=24)			
Age								
Range	21 – 35		22 – 34		21 – 34		F=1.227	0.300
Mean ± SD	27.04 ± 4.13		28.54 ± 4.28		26.75 ± 4.34			
Residence								
Rural	15	62.5	12	50.0	15	62.5	χ^2=1.029	0.598
Urban	9	37.5	12	50.0	9	37.5		
Occupation								
Not working	11	45.9	15	62.5	12	50.0	χ^2=1.449	0.485
Working	13	54.1	9	37.5	12	50.0		
Weight								
Range	63 – 89.5		65.5 – 89.5		66 – 88.5		F=0.154	0.857
Mean ± SD	76.77 ± 7.64		75.73 ± 6.48		76.25 ± 5.12			
Height								
Range	158 – 173		160 – 172		159 – 172		F=0.280	0.757
mean ± SD	166 ± 4.75		166.42 ± 3.44		166.88 ± 3.86			
BMI								
Range	24.2 – 31		24.2 – 31		24.7 – 30.3		F=0.421	0.658
Mean ± SD	27.8 ± 1.78		27.35 ± 2.08		27.4 ± 1.77			

Table 2: Comparison between the studied cases as regard Ultrasound Biometry.

	Studied cases			Test	P
	LMWH group (n=24)	ASA group (n=24)	Control (n=24)		
Femur Length					
Range	61 – 77	60 – 77	60 – 77	F=0.782	0.461
Mean ± SD	72.92 ± 4.1	72.38 ± 3.32	71.5 ± 4.38		
Biparetal diameter					
Range	81 – 100	88 – 100	84 – 100	F=2.556	0.085
Mean ± SD	91.38 ± 4.84	94.04 ± 4.19	93.71 ± 4.3		
Head Circumference					
Range	301 – 360	308 – 360	308 – 359	F=0.657	0.522
Mean ± SD	340.83 ± 14.49	338.58 ± 14.79	336.08 ± 13.8		
Abdominal circumference					
Range	277 – 354	277 – 356	273 – 356	F=0.480	0.621
Mean ± SD	322.58 ± 20.68	325.83 ± 19.95	328.42 ± 21.34		
EFW (Kg)					
Range	1.8 – 4.3	2 – 4.2	2 – 4.1	F=0.842	0.435
Mean ± SD	3.14 ± 0.66	3.3 ± 0.57	3.07 ± 0.61		

F: One-way ANOVA, p: p value for comparing between different categories**,** *: Statistically significant at $p \leq 0.05$.

Table 3: Comparison between the studied cases as regard Doppler US.

	Studied cases			Test	P
	LMWH group (n=24)	ASA group (n=24)	Control (n=24)		
UA PI					
Range	0.7 – 1.6	0.9 – 1.5	0.8 – 1.7	F=1.672	0.195
Mean ± SD	1.18 ± 0.27	1.18 ± 0.2	1.3 ± 0.31		
UA S/D					
Range	2.6 – 3.5	2.5 – 3.8	2.7 – 3.8	F=2.432	0.095
Mean ± SD	3.07 ± 0.34	3.28 ± 0.45	3.27 ± 0.34		
MCA PI					
Range	1.6 – 2.3	1.5 – 2.3	1.5 – 2.5	F=0.657	0.377
Mean ± SD	1.98 ± 0.2	1.98 ± 0.25	2.08 ± 0.32		
MCA PSV					
Range	30.4 – 55.5	26.8 – 48.3	28.5 – 59.6	F=3.404	0.039*
Mean ± SD	44.88 ± 7.2	39.96 ± 6.05	44.55 ± 8.48		
UtA PI					
Range	0.7 – 1.4	1.0 – 1.8	0.8 – 1.6	F=16.356	<0.001*
Mean ± SD	1.04 ± 0.23	1.45 ± 0.26	1.15 ± 0.29		

F: One-way ANOVA, p: p value for comparing between different categories**,** *: Statistically significant at $p \leq 0.05$.

Table 4: Comparison between the studied cases as regard maternal complications.

	Studied cases						Test	P
	LMWH group (n=24)		ASA group (n=24)		Control (n=24)			
Miscarriage								
No	24	100.0	24	100.0	24	100.0	—	—
Preterm delivery								
No	20	83.3	21	87.5	22	91.7	χ^2=0.762	0.683
Yes	4	16.7	3	12.5	4	8.3		
Post-partum Hemorrhage								
No	18	75.0	21	87.5	22	91.7	χ^2=2.790	0.248
Yes	6	25.0	3	12.5	2	8.3		

χ^2: Chi-square test, p: p value for comparing between different categories**,** *: Statistically significant at $p \leq 0.05$.

Table 5: Comparison between the studied cases as regard neonatal outcome.

	Studied cases						Test	P
	LMWH group (n=24)		ASA group (n=24)		Control (n=24)			
IUGR								
No	21	87.5	22	91.7	21	87.5	χ^2=281	0.869
Yes	3	12.5	2	8.3	3	12.5		
Apgar 1								
Range	5 – 9		5 – 9		5 – 9		F=0.115	0.892
Mean ± SD	6.96 ± 1.4		6.75 ± 1.39		6.83 ± 1.74			
Apgar 5								
Range	5 – 10		5 – 10		6 – 10		F=0.017	0.98.
Mean ± SD	8.21 ± 1.53		8.17 ± 1.76		8.25 ± 1.36			

F: One-way ANOVA, χ^2: Chi-square test, p: p value for comparing between different categories, *: Statistically significant at $p \leq 0.05$.

Table 6: Prognostic performance for ROC curve for MCA PSV prediction of unfavorable fetal outcomes.

	AUC	p	95% C. I	Sensitivity	Specificity	PPV	NPV
MCA PSV	0.814	0.018*	0.566 – 1.062	84.62	83.33	95.7	55.6

AUC: Area Under a Curve, p value: Probability value, CI: Confidence Intervals, NPV: Negative predictive value PPV: Positive predictive value, *: Statistically significant at $p \leq 0.05$

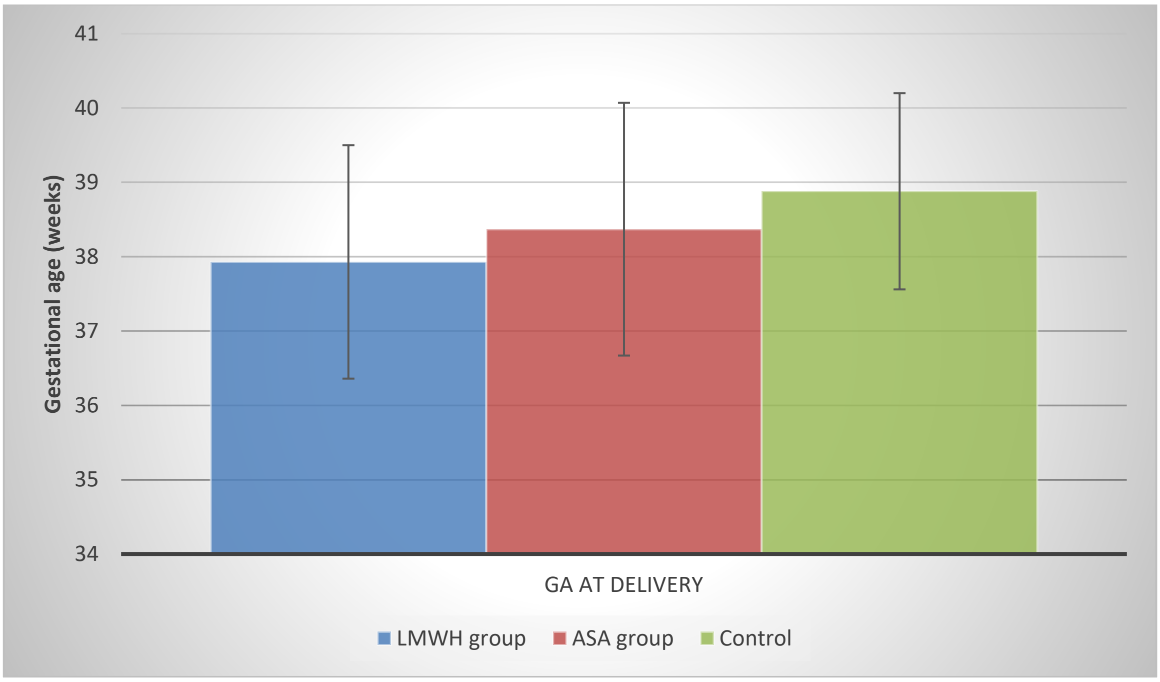

Figure 1: Comparison between the studied cases as regard GA at delivery.

CPR was an excellent predictor tool for neonatal outcome in severe hypertension pregnant women and may be used to identify fetuses at risk of morbidity or fatality, as shown by El-Demiry et al., (2020) [7]. We also found that babies who were born with improper CPR had lower birth weights, worse APGAR scores at 5 minutes, a greater rate of admission to the neonatal intensive care unit (NICU), a longer hospital stay, and a higher rate of perinatal mortality. This proportion takes into account the fact that "brain sparing" and vasodilation reduce MCA resistance while increasing umbilical artery resistance due to placental malfunction. Three percent of infants had IUGR, ten percent were born small for gestational age, and two percent were stillborn because the uterus ruptured after delivery, as shown in a study by Bremme et al., (2021) [12]. The Apgar score was available for only one kid (2%).

4. Conclusions

The doppler indices ratio of the middle cerebral to the umbilical arteries is useful in predicting fetal well-being and newborn outcome in pregnant women receiving thromboprophylaxis between 28 and 34 weeks of gestation. To determine the best course of therapy for this diverse patient population, large prospective randomized studies are needed.

References

[1] S. M. Bates, S. Middeldorp, M. Rodger, A. H. James, I. Greer. (2016). Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. Journal of thrombosis and thrombolysis. 41: 92-128.

[2] A. Rossi. (2015). Evaluation of fetal cerebral blood flow perfusion using three-dimensional power doppler ultrasound angiography in fetuses affected by intrauterine growth retardation.

[3] E. Meler, J. Martínez, D. Boada, E. Mazarico, F. Figueras. (2021). Doppler studies of placental function. Placenta. 108: 91-96.

[4] H. Figueroa-Diesel, E. Hernandez-Andrade, R. Acosta-Rojas, L. Cabero, E. Gratacos. (2007). Doppler changes in the main fetal brain arteries at different stages of hemodynamic adaptation in severe intrauterine growth restriction. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 30 (3): 297-302.

[5] P. P. Jaiprakash. (2020). Cerebro Placental Ratio at 30–34 Weeks' Gestation in the Prediction of Perinatal Outcome in Low Risk and High-Risk Pregnancy (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).

[6] C. Hui, M. Lili, C. Libin, Z. Rui, G. Fang, G. Ling, Z. Jianping. (2012). Changes in coagulation and hemodynamics during pregnancy: a prospective longitudinal study of 58 cases. Archives of gynecology and obstetrics. 285: 1231-1236.

[7] N. M. El-Demiry, A. M. Maged, H. M. Gaafar, S. ElAnwary, A. Shaltout, S. Ibrahim, M. M. Elsherbini. (2020). The value of fetal Doppler indices as predictors of perinatal outcome in women with preeclampsia with severe features. Hypertension in Pregnancy. 39 (2): 95-102.

[8] N. Riyazi, M. Leeda, J. I. de Vries, P. C. Huijgens, H. P. van Geijn, G. A. Dekker. (1998). Low-molecular-weight heparin combined with aspirin in pregnant women with thrombophilia and a history of preeclampsia or fetal growth restriction: a preliminary study. European Journal of Obstetrics &

Gynecology and Reproductive Biology. 80 (1): 49-54.
[9] Z. Alfirevic, T. Stampalija, T. Dowswell. (2017). Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane database of systematic reviews. 6.
[10] A. Khalil, B. Thilaganathan. (2017). Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term. Best practice & research Clinical obstetrics & gynecology. 38: 38-47.
[11] J. Bar, R. Mashiah, B. Cohen-Sacher, M. Hod, R. Orvieto, Z. Ben-Rafael, J. Lahav. (2001). Effect of thrombophylaxis on uterine and fetal circulation in pregnant women with a history of pregnancy complications. Thrombosis research. 101 (4): 235-241.
[12] K. Bremme, A. Lannemyr, L. Tyni, R. Chaireti. (2021). Obstetric and neonatal outcomes in pregnant women treated with high-dose thromboprophylaxis: a retrospective, single-center study. The Journal of Maternal-Fetal & Neonatal Medicine. 34 (10): 1641-1644.