LOWER EXTREMITY VENOUS DOPPLER FLOW IN PREGNANCIES WITH AND WITHOUT PRE-ECLAMPSIA IN THE THIRD TRIMESTER

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MASTER OF MEDICINE

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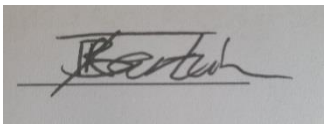
This research report is submitted to the University of the Witwatersrand Health Sciences Faculty in the submissible format in partial fulfilment of the degree of Master of Medicine in Obstetrics and Gynaecology in June 2022.

DECLARATION

I, Rori Fortuin declare that this work is original and contains no section copied in whole or in part from any other source, unless explicitly identified in quotation marks and with detailed, accurate referencing. I declare that this work has not been submitted before to this or any other University for the purposes of a post graduate degree.



Signed 14 June 2022

DEDICATION

I dedicate this Masters to my parents, Fiona and Newton, who have always encouraged me, and to my ever-supportive fiancé, Matthew Gibb.

ABSTRACT

The aim of this study is to describe and compare lower extremity venous Doppler flow in normal pregnancies and women with pre-eclampsia in the third trimester. It was a prospective case control study that took place at Rahima Moosa Mother and Child Hospital with 100 participants recruited from the antenatal wards between February and November 2020. 50 participants were allocated to the group with pre-eclampsia and the remaining normotensive participants to the control group. Each participant completed a questionnaire and underwent ultrasonographic assessment of four of the veins of the lower limbs bilaterally. Main outcome measures included spontaneous blood flow echogenicity, doppler waveform, compressibility and diameter of veins. Results showed significant differences for six of the eight veins measured for spontaneous blood flow echogenicity in the lower grades ($p < 0.001$). Patients with pre-eclampsia have microcirculatory vessel changes that are believed to be associated with slower blood flow and predisposition towards stasis and clotting, however our results showed otherwise. The diameter of the small saphenous vein on the left was significantly smaller in pre-eclamptic patients as opposed to the control group ($p = 0.026$). In conclusion, our study produced insufficient evidence to suggest that pregnant women with pre-eclampsia are at increased risk of developing VTE using this screening method as our results showed normal blood flow echogenicity in both groups. Because of its association with a hypercoagulable state and increased rate of thrombotic events, spontaneous blood flow echogenicity may potentially be a marker of thromboembolic risk thus we suggest a larger prospective study in combination with an objective test of blood flow velocity to adequately assess the significance of this phenomenon.

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LIST OF ABBREVIATIONS

ACOG	-	American College of Obstetricians and Gynecologists
ANC	-	Antenatal Care
BMI	-	Body Mass Index
BP	-	Blood pressure
CFV	-	Common femoral vein
DFV	-	Deep femoral vein
DIC	-	Disseminated intravascular coagulopathy
DVT	-	Deep vein thrombosis
FV	-	Femoral vein
HIV	-	Human Immunodeficiency Virus
ISSHP	-	International Society for the study of Hypertension in Pregnancy
LMWH	-	Low Molecular Weight Heparin
NETS	-	Neutrophil extracellular traps
PE	-	Pulmonary embolism
POP	-	Popliteal vein
RCOG	-	Royal College of Obstetricians and Gynaecologists
SOGC	-	Society of Obstetricians and Gynaecologists of Canada
SSV	-	Small saphenous vein
UFH	-	Unfractionated Heparin
VTE	-	Venous thromboembolism

JOURNAL ARTICLE

Lower extremity venous doppler flow in pregnancies with and without pre-eclampsia in the third trimester

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Abstract

Objective: This study aims to describe and compare lower extremity venous Doppler flow in normal pregnancies and women with pre-eclampsia in the third trimester.
Study design: Prospective case control study involving pregnant women in their third trimester with 50 normotensive women belonging to the control group and 50 women with pre-eclampsia. Each woman underwent ultrasonography of the lower limb veins.
Main outcome measures: Demographics, spontaneous blood flow echogenicity, Doppler waveform, compressibility and diameter of veins of both lower limbs.
Results: Significant differences were observed for five of the eight veins measured for spontaneous blood flow echogenicity ($p<0.001$), with pre-eclamptic patients scoring mostly grade 0 as opposed to the control group scoring grade 1. The diameter of the small saphenous vein on the left was also significantly smaller in pre-eclamptic patients as opposed to the control group ($p=0.026$).
Conclusion: Our study produced insufficient evidence to suggest that pregnant women with pre-eclampsia are at greater risk of developing VTE using this screening method as our results showed normal blood flow echogenicity in both groups.
Keywords: Pre-eclampsia, Deep Vein Thrombosis, Thromboprophylaxis, Lower limb venous Doppler, Spontaneous blood flow echogenicity

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1. Introduction

Pregnancy is associated with changes in venous function that result in an increased incidence of venous disease [1] including venous thromboembolism (VTE), manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE), and varicose veins. In the general population the incidence of VTE in pregnancy and the puerperium is approximately 1 in 1000-2000 deliveries, with the risk being more than five times greater than in non-pregnant women of comparable age [2-4]. Although this value appears to be infrequent with a low absolute value, it is a serious and potentially fatal condition and is a prominent cause of maternal morbidity and mortality during this period [4].

In pregnancy, nearly all procoagulants are increased, creating a state in which equilibrium is shifted toward coagulation [5,6]. Egan et al. [7] alludes to the risk of VTE in women with pre-eclampsia being up to 5-fold greater than that of the general pregnant population, especially in those with severe or early onset pre-eclampsia. This risk may further extend from 6 to 12 weeks postpartum . Potential mechanisms identified include endothelial activation, platelet activation, coagulation activation and inflammation, however the precise cause of this elevated thrombotic risk remains unclear [7].

Venous compression ultrasonography with Doppler studies has become the imaging test of choice for diagnosis of DVT in the lower extremities [8,9] with 97 percent sensitivity for detecting DVT in the popliteal and femoral veins [10].

The question that remains controversial is whether to use prophylactic anticoagulants during pregnancy and the puerperium to prevent the development of VTE and its severe consequences. This is a challenging topic due to the potential for

complications to both the fetus and mother. The decision to start anticoagulation prophylaxis during pregnancy is based on determining the risk to benefit ratio and finding equilibrium between the predicted risk of VTE, the reduced risk if given prophylaxis, as well as the burden accompanying the use of anticoagulants [4].

All women should therefore undergo a personalised evaluation of risk for VTE at the time of confirmation of pregnancy, and again should new clinical situations arise during the pregnancy. Furthermore, should patients present with symptoms of the development of VTE, Doppler ultrasound may assist with confirming the diagnosis and need for anticoagulation [4].

There is a paucity of literature to establish normal parameters in lower limb venous blood flow during pregnancy, using ultrasonography, and even less so with pre-eclampsia. The purpose of this study is thus to describe the ultrasonographic features of the lower limb veins in order to establish potential norms as well as compare these findings with that of pre-eclamptic patients. A comparison between patients with normal physiology and those with anticipated vascular dysfunction, as can be seen in patients with pre-eclampsia, may assist with identifying patients at risk of developing VTE disease in pregnancy. The objective here is to assist with risk stratification and identification of patients that may benefit from prophylactic anticoagulation in pregnancy, by addressing the risk to benefit ratio in conjunction with additional risk factors for VTE.

The aim of the study is to describe and compare lower extremity venous Doppler flow in pregnancies with and without pre-eclampsia in the third trimester, with the following objectives:

1. To describe the demographics and clinical characteristics of patients undergoing doppler ultrasound of the lower extremities, and further describe mode of delivery, gestational age at delivery as well as describe short-term outcomes relating to birth APGAR scores and weight.
2. To compare spontaneous blood flow echogenicity of lower extremity veins in normal pregnancies in the third trimester with that of pre-eclamptic women, by using a grading system.
3. To compare venous doppler wave forms of lower extremity veins in normal pregnancies in the third trimester with that of pre-eclamptic women, to assess patency of the vessels.
4. To compare diameters of lower extremity veins in normal pregnancies in the third trimester with those of pre-eclamptic women.
5. To compare the compressibility of lower extremity vein walls in normal pregnancies in the third trimester with that of pre-eclamptic women.

2. Materials and methods

Study design and population

One hundred participants in their third trimester of pregnancy were recruited for this prospective case control study between February and November 2020 at Rahima Moosa Mother and Child Hospital. Fifty participants diagnosed with pre-eclampsia according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines [11] and 50 normotensive participants allocated to the control group were recruited from the antenatal wards with the stratified sampling method. Approval was obtained from the Human Research Ethics Committee (medical) with a clearance certificate number of M190964. Informed consent was obtained pre-intervention and anonymity was maintained.

All participants were asymptomatic for VTE with singleton pregnancies between 27 and 41 completed weeks gestation determined by early ultrasound or by sure dates of last normal menstrual period, with no observed malformations of the fetus. Exclusion criteria were cigarette smoking history, previous venous thromboembolism, history of pre-pregnancy medical conditions known to impact vascular function such as diabetes mellitus, hypertension, autoimmune disorders, cardiac disease and human immunodeficiency virus. Pre-eclamptic patients were treated with aldomet and amlodipine antihypertensive agents.

Patients were recruited from the antenatal ward and antenatal clinic. Due to the time constraints with the sonographer's schedule, a maximum of two assessments per day on only two to three days per week was feasible. As a result, it was often not possible to recruit patients on the same day as assessment as the sonographer's schedule was unpredictable. Therefore, the majority of patients were recruited from the antenatal wards a day in advance. These patients were admitted for various reasons including to await elective caesarean section and induction of labour.

Assessments

Each participant was examined once using a Philips EPIQ 5 Colour Doppler Ultrasound System with a high frequency L12-3, 50 Hz linear array probe and 50 Hz Doppler with the option of steering the colour box to an acceptable angle for optimal Doppler shift recording. All the procedures were performed by one qualified ultrasonographer who is experienced in performing ultrasound studies on patients with suspected DVT.

Participants were positioned on their left side with the left lower limb straight, and the right side elevated obliquely by 20 degrees. The right lower limb was supported by a

soft pillow to keep the knee flexed to 60 degrees, and the upper body elevated by 15 degrees [1,12] in order to ensure measurements were made at the level of the right atrium of the heart. Participants were tilted in reverse Trendelenburg position to encourage venous distension and limit compression of the inferior vena cava [13].

The measurements of vein diameter, compressibility, waveform and spontaneous blood flow echogenicity were assessed after ten minutes rest on both left and right lower limbs. Each leg was imaged from the saphenofemoral junction to the ankle at the following points, with minimal pressure applied to the skin to avoid venous compression [14]:

i. Common femoral vein (CFV), 10cm below the saphenofemoral junction.
ii. Femoral vein (FV), 5cm below the junction forming the CFV.
iii. Popliteal vein (POP), at the level of the popliteal fossa skin crease.
iv. Small saphenous vein (SSV), 5cm below its junction with the popliteal vein.

Outcome measures

1. Demographics, including age, parity, height and weight at ANC booking, previous deliveries and medical conditions were obtained from participant antenatal cards.
2. The grading of spontaneous blood flow echogenicity was as follows [12]:

    Grade 0 - Anechoic (absent)
    Grade 1 - Barely visible echoes
    Grade 2 - Clearly visible echoes whose intensity remains lower than that of surrounding tissues
    Grade 3 - Blood flow echogenicity equal to or greater than that of surrounding tissues (Hyperechoic)
3. Waveforms were assessed using pulsed-wave Doppler, following augmentation by squeezing the extremity distally [14] and were categorised as follows:

    Triphasic - forward flow in systole; reverse flow in late systole or early diastole; forward flow in late diastole.

Biphasic - reverse flow in diastole; steady positive flow in the diastole, or forward flow in systole.

Monophasic - single phase with slow flow (acceleration or deceleration).

Flat - Non-pulsatile

4. The diameters were measured in millimetres using electronic calipers at the four sites mentioned. They were measured transversely in the longitudinal section, from wall to wall, ignoring luminal irregularities [12,15].
5. Compressibility of veins was assessed and graded as either ‘yes’, ‘no’ or partially compressible, to assess the formation of thrombi in the veins [10].

Statistical analysis

Statistical analyses were conducted in R software (version 4.00; www.R-project.org). The normal distribution of the data was checked using the Shapiro–Wilk test and examining Q-Q plots. Comparisons between the two groups (pre-eclamptic vs control) for categorical data were analysed using Pearson’s chi-squared contingency tests (with Yates correction, where appropriate). Statistical differences for continuous variables were analysed using Welch’s t-test for parametric data and Mann-Whitney U tests or Wilcoxon matched pairs tests for non-parametric data. Tests were two-tailed and model significance set at 0.05.

Data was reported as frequencies and percentages (categorical variables) or mean ($\pm$SD) and median with interquartile ranges (continuous variables), as appropriate, and are presented descriptively in charts, tables or in text. The sample sizes were 50 pre-eclamptic and 50 control participants. This sample size was not determined by a power calculation but rather as a convenient size for a preliminary investigation. We recognise the limitation that the study is unlikely to be powered to detect a significant difference.

3. Results

Demographics

Table 1 represents the differences in demographics and clinical characteristics between the pre-eclamptic and control groups. There were no significant differences in age, height and weight however, pre-eclamptic patients had a significantly higher BMI (6%, $p = 0.041$) than control patients (Table 1). Pre-eclamptic patients showed significantly earlier gestational ages at recruitment (26 days, $p < 0.001$) and at delivery (27 days, $p < 0.001$) than control patients. In addition, the neonates of the pre-eclamptic group women were significantly lighter (mean 932g, $p < 0.001$) than those of control group women.

Three of the 100 participants delivery information were not obtained due to their files not being located. For the mode of delivery, 38 (76%) of pre-eclamptic and 29 (58%) control group patients delivered via caesarean section whereas 10 (20%) pre-eclamptic and 20 (40%) control group patients had a normal vaginal delivery. There was a trend towards significance ($p=0.056$) in favour of more caesarean deliveries in pre-eclamptic patients.

Poor clinical outcomes in the study included two stillbirths, one in the pre-eclamptic group at 34 weeks, and the other at 30 weeks gestation from the control group. The latter was the only participant diagnosed with a DVT and was started on anticoagulation. She was diagnosed with placenta previa major, and subsequently developed significant antepartum haemorrhage resulting in the stillbirth of her baby. She was asymptomatic for VTE thus the diagnosis of DVT on ultrasound assessment was an incidental finding. The other stillbirth was due to abruptio placenta. Another control group patient underwent a total abdominal hysterectomy

for severe postpartum haemorrhage following a retained placenta post normal vaginal delivery at 40 weeks gestation.

Table 1. Demographic and clinical data.

Variables	**Groups**	**Values**	**Statistics**
Age (years)	Pre-eclamptic	30.62 (±6.49)	df = 97.68 p = 0.271
	Control	29.14 (±6.88)	
Height (m)	Pre-eclamptic	1.59 (±0.06)	df = 97.70 p = 0.810
	Control	1.60 (±0.06)	
Weight (kg)	Pre-eclamptic	76.84 (±20.05)	df = 91.38 p = 0.152
	Control	71.70 (±15.21)	
BMI (kg/m^2)	Pre-eclamptic	30.33 (±7.10)	U = 954 p = 0.041*
	Control	28.40 (±5.11)	
Parity	Pre-eclamptic	1.42 (±1.13)	U = 1221.5 p = 0.842
	Control	1.42 (±1.31)	
Gravidity	Pre-eclamptic	2.78 (±1.59)	U = 1232.5 p = 0.9045
	Control	2.72 (±1.53)	
Gestational age at recruitment (days)	Pre-eclamptic	238.66 (±27.37) – 34.1 weeks	df = 97.97 p < 0.001*
	Control	264.38 (±26.86) – 37.8 weeks	
Gestational age at delivery (days)	Pre-eclamptic	244.17 (±22.05) – 34.9 weeks	df = 94.83 p < 0.001*
	Control	271.35 (±21.58) – 38.8 weeks	
Birth weight (g)	Pre-eclamptic	2117.98 (±755.54)	df = 94.95 p < 0.001*
	Control	3049.69 (±754.55)	
APGAR (1 min)	Pre-eclamptic	8.3 (±1.69)	U = 1116.5 p = 0.585
	Control	8.06 (±1.96)	
APGAR (5 min)	Pre-eclamptic	9.54 (±1.54)	U = 1200 p = 0.798
	Control	9.51 (±1.63)	
Values are mean (±SD). * p-value < 0.05 depicts statistical significance. Statistics used: Welch's t-test and Mann-Whitney U tests.			

Spontaneous blood flow echogenicity

Spontaneous blood flow echogenicity was assigned to one of four grade scores for each of the eight veins (Figure 1). Pairwise comparisons between the two groups were conducted with significant differences observed in five of the eight veins (Table 2). For these five veins, significantly more pre-eclamptic patients were scored as grade 0 as opposed to significantly more control patients being scored as grade 1.

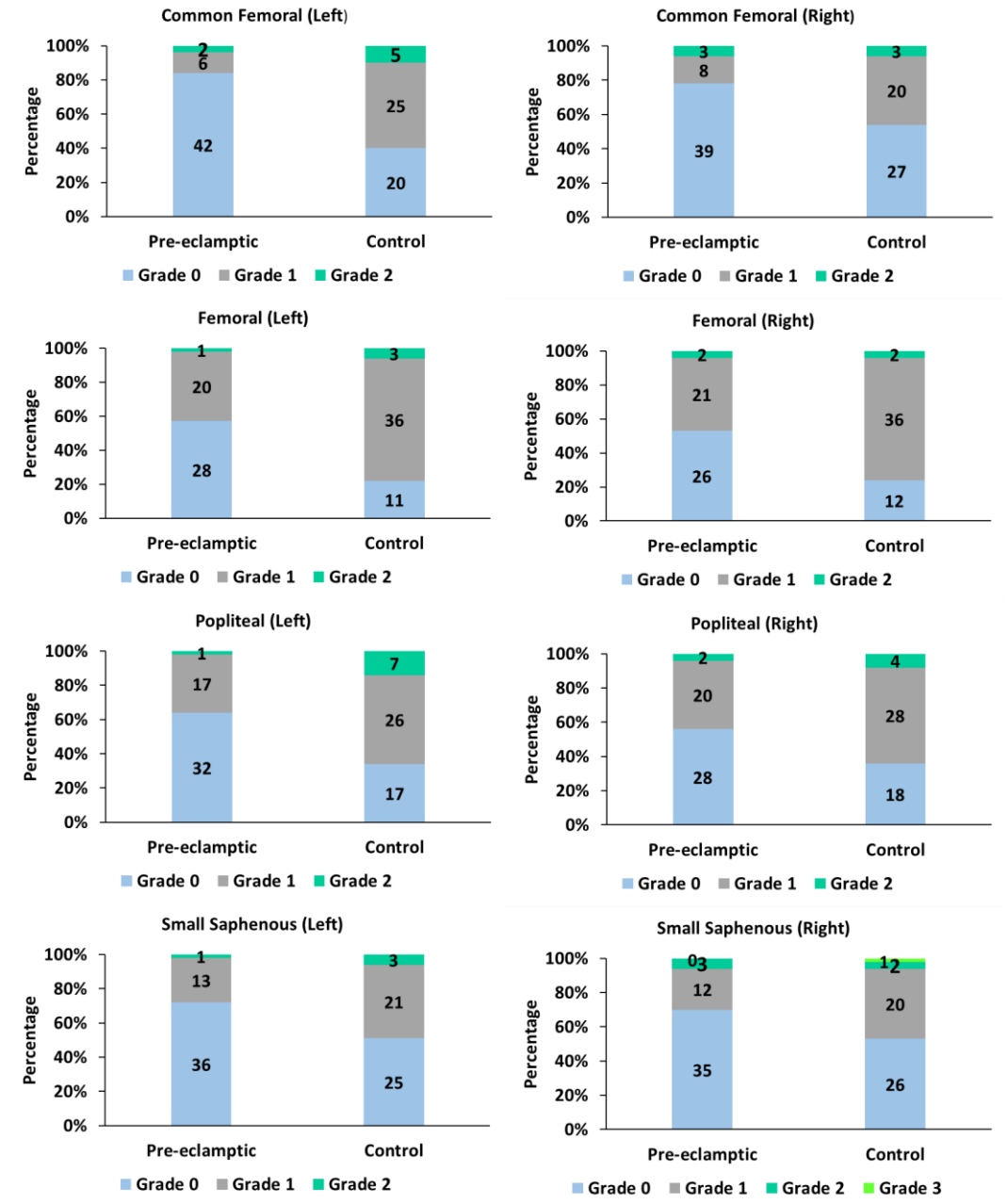

Figure 1. Distribution of grades of spontaneous blood flow echogenicity between groups

Waveform

The waveform types were assessed in one of four categories for the eight veins, with no statistically significant differences observed between the two groups (Table 2). In all veins, monophasic waveforms were common and similarly distributed in pre-eclamptic and control groups, except for the small saphenous vein, in which flat waves were common (Figure 2).

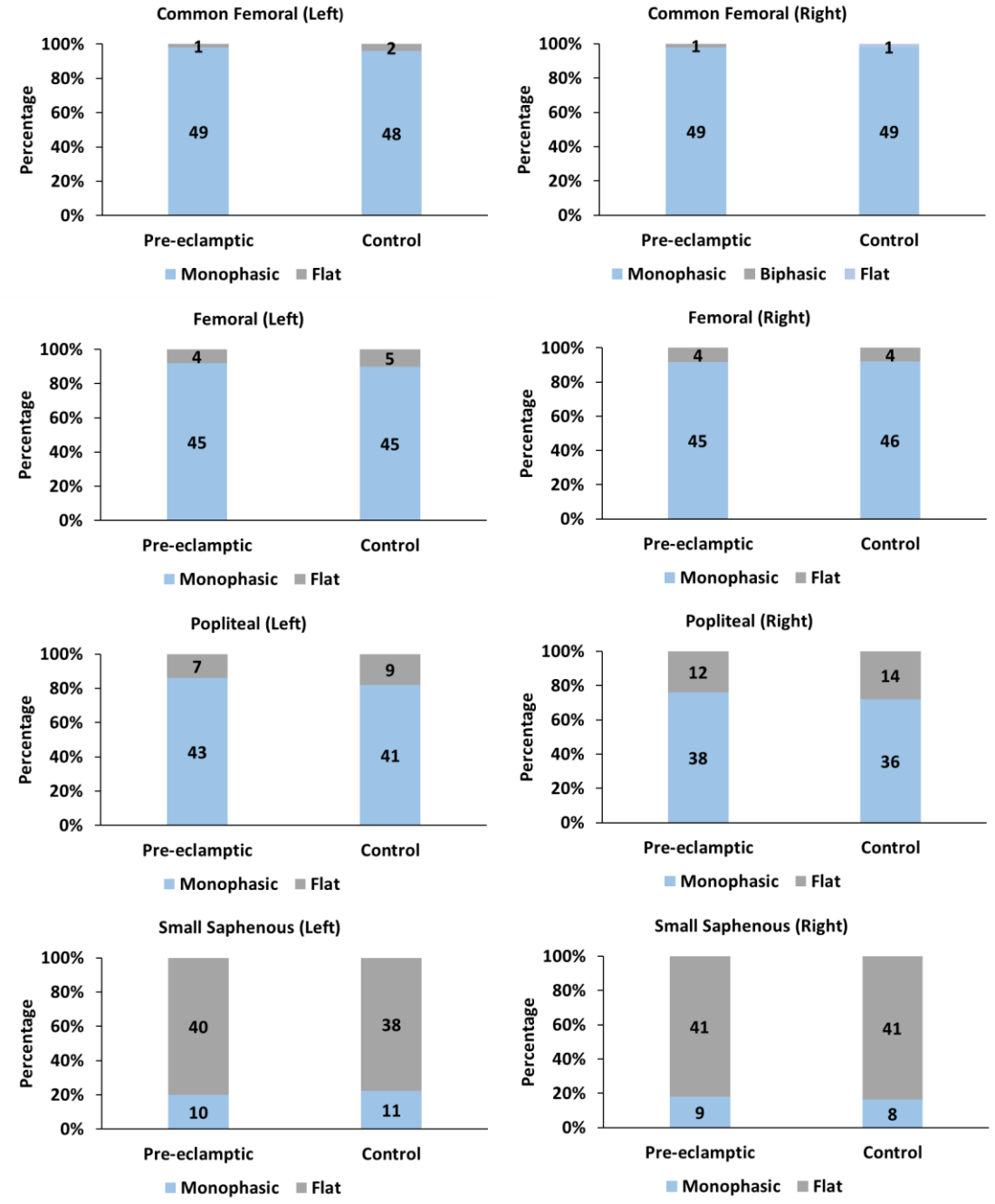

Figure 2. Distribution of waveform types between groups.

Diameter

A significant difference was noted only in the diameter of the small saphenous (left) vein, which was smaller in pre-eclamptic than control patients (Figure 3). Vein diameter did not differ significantly for the remaining seven veins (Table 2).

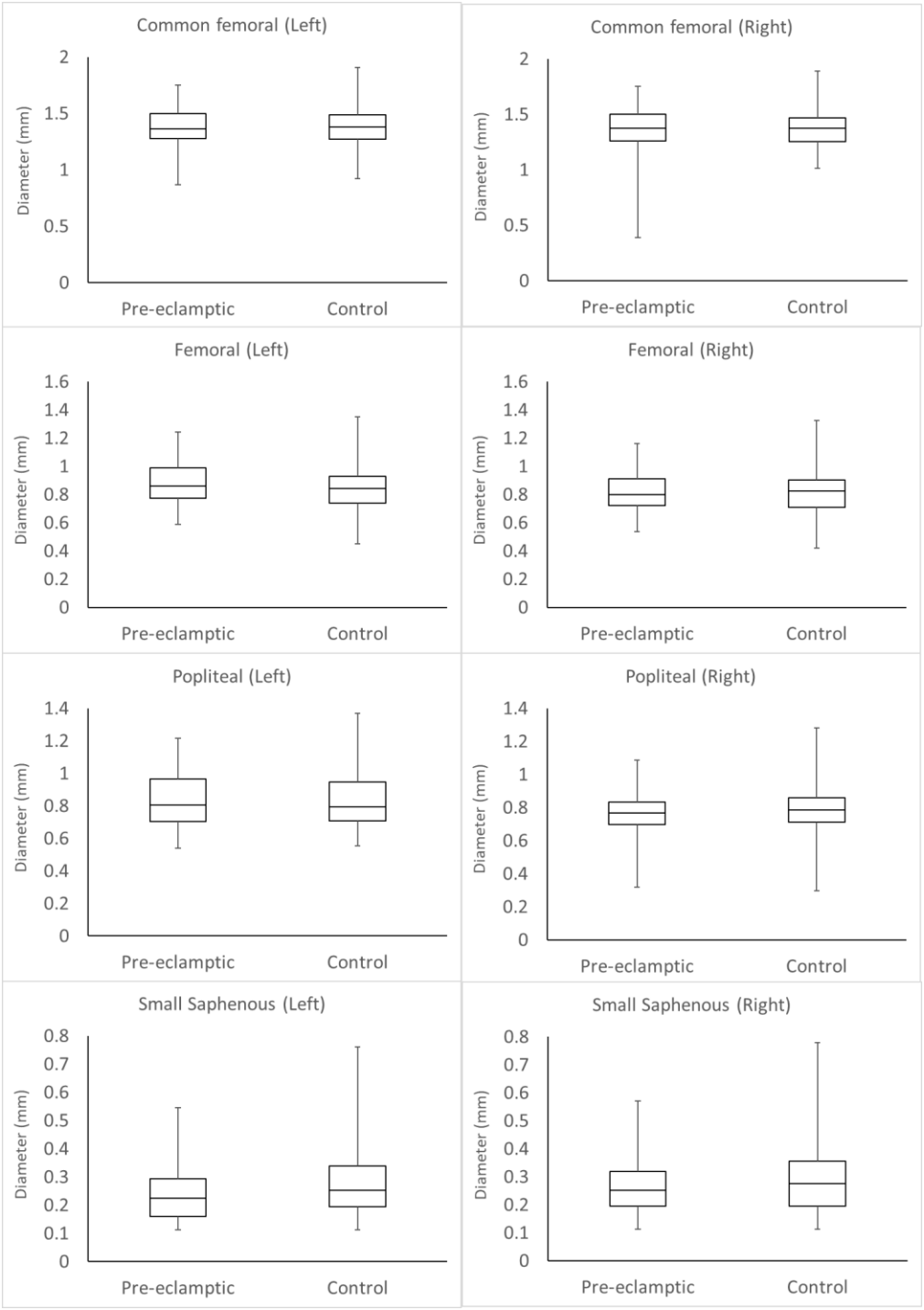

Figure 3. Comparison of diameters for each vein depicting the median, 1st and 3rd interquartiles, minimum and maximum scores.

Table 2. P-values depicting comparison between control and pre-eclamptic groups

			Spontaneous blood flow echogenicity	Waveform	Diameter
1.	**Common femoral vein**	Left	< 0.001*	1.000	0.989
2.		Right	0.026*	0.368	0.923
3.	**Femoral vein**	Left	0.006*	1.000	0.233
4.		Right	0.011*	1.000	0.812
5.	**Popliteal vein**	Left	0.004*	0.785	0.986
6.		Right	0.124	0.820	0.565
7.	**Small saphenous vein**	Left	0.088	0.958	0.026*
8.		Right	0.211	1.000	0.564
* p-value < 0.05 describing statistical significance between groups					

Compressibility

All eight veins were compressible in both pre-eclamptic and control groups. The one control participant diagnosed with a partial thrombus in the left common femoral and femoral veins also had partially compressible veins.

4. Discussion

The blood vessel lumen is usually free of internal echoes during ultrasonography [16] and presents as anechoic [17]. However, internal echoes have been demonstrated in venous blood flow, described with varying degrees of echogenicity. Machi et al. [16] explains the mechanism to be related to three factors, namely the presence of circulatory red cell aggregates, macromolecules such as fibrinogen that are increased in states of prolonged stasis, as well as increased temperatures. Reduced shear rates favour red cell aggregation with low velocity blood in a vein of larger diameter having a greater tendency toward red cell aggregation. This phenomenon should not be confused with thrombosis as it occurs frequently in conditions of slow venous flow [17]. It is however associated with a state of hypercoagulation with a greater frequency of thromboembolic events [18] and thus may potentially be a marker of thromboembolic risk.

Rabhi et al. [12] studied spontaneous blood flow echogenicity in pregnancy and noted a gradual increase as the pregnancy advanced with 96% of pregnancies showing clearly visible (Grade 2) or marked (Grade 3) blood flow echogenicity in the third trimester. On the other hand, spontaneous blood flow echogenicity was absent (Grade 0) or barely visible (Grade 1) in 94% of pregnancies during the first trimester. They concluded that the presence of these echoes is a normal finding in advanced pregnancy. This is however the only study of its kind assessing blood flow echogenicity in this manner with a grading system in pregnancy.

Our study aimed to detect differences between the lower limb vein parameters in pregnant women with and without pre-eclampsia. In contrast to the previous study mentioned, we found that in the third trimester, majority of patients in both groups had spontaneous blood flow echogenicity in the lower grades (0 and 1) (Figure 1). Furthermore, in five of the eight veins, the pre-eclamptic group showed majority grade 0 spontaneous blood flow echogenicity.

In contrast with our findings, we had expected to find higher grades of echogenicity in this population group where alterations in microcirculatory flow distribution, characterised by sluggish and intermittent flow, occur [19]. This difference may potentially have been affected by the significantly earlier gestational age at recruitment and delivery of the pre-eclamptic group by approximately one month. With reference to Rabhi et al. [12], where spontaneous blood flow echogenicity grade increases as the pregnancy progresses, it is possible that the grade may have progressed further should the pregnancy have continued.

The significantly earlier gestational age at recruitment and delivery, with associated lower birth weights, in the pre-eclamptic group is due international recommendations

of delivery at diagnosis of severe pre-eclampsia at and beyond 34 weeks gestation as opposed to expectant management prior to this time. Planned early delivery is recommended due to the lower risk of composite maternal mortality and severe morbidity [20,21].

Normal venous flow in the larger peripheral veins is spontaneous with low velocity. The smaller distal veins have even lower velocity and may not produce discernible Doppler signals in the resting state. Peripheral veins that are most distal to the heart demonstrate less spontaneity and lack pulsatile flow as seen in veins closer to the heart. This explains why the most distal small saphenous veins show flat waveforms with less spontaneous blood flow and venous stasis. The remaining proximal monophasic waveform patterns represent low-resistance blood flowing in a single direction with continuous forward flow for the duration of the cardiac cycle. [22] Both of these waveforms can thus be described as normal in the lower limbs.

There is an overall inclination for all lower extremity veins to progressively distend throughout pregnancy, attaining a peak at term [13]. The difference in diameter for the short saphenous vein, with the left vein being smaller in the pre-eclamptic group may be attributed to vasoconstriction observed in the veins of pre-eclamptic patients. Deep venous thrombosis (DVT) is known to be more prominent in the left leg of the deep venous system [2,3], however isolated thrombosis in the distal veins are of uncertain significance as they occur infrequently in pregnancy [9]. The fact that this difference was only observed in one of eight veins makes it a coincidental finding. In addition, the use of antihypertensive medication with vasodilatory effects used in the pre-eclamptic group had no effect venous diameters measured.

Our study had some limitations in design. Firstly, the use of a grading system for spontaneous blood flow echogenicity with limited previous use resulted in minimal data with which to compare our study. Secondly, we only looked at women once in the third trimester of pregnancy and did not repeat the assessment, particularly in the postpartum period where risk of VTE is at its highest. A comparative assessment of all three trimesters as well as the postpartum period is recommended to adequately assess the changes that occur throughout these phases. Thirdly, spontaneous blood flow echogenicity is a subjective test, we did however control for interobserver variability [18]. We suggest a larger prospective study in combination with an objective test, such as that of blood flow velocity, to adequately assess the significance of this phenomenon.

5. Conclusion

In conclusion, our study produced insufficient evidence to suggest that pregnant women with pre-eclampsia are at greater risk of developing VTE using Doppler ultrasound as a screening method as our results showed similar characteristics in both groups.

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Declaration of interests

There are no competing interests to declare.

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Appendix A: Approved Protocol

1. INTRODUCTION

Pregnancy is associated with changes in venous function that result in an increased incidence of venous disease[1], including venous thromboembolism (VTE), which may manifest as deep vein thrombosis (DVT) or pulmonary embolism (PE), and varicose veins.

In the general population the incidence of VTE in pregnancy and the puerperium is estimated to be between 1 in 1000-2000 deliveries, with the risk being more than five times greater than in non-pregnant women of comparable age [2-4]. Although this value appears to be infrequent with a low absolute value, it is a serious and potentially fatal condition and is a leading cause of maternal morbidity and mortality during this period[4].

According to Dresang et al.[5], DVT occur with equal frequencies in all trimesters and the postpartum period. Coriu et al.[6] however, found the incidence of VTE to be increasing with each trimester, with the greatest incidence occurring during the puerperium. Bates et al.[4] add that the daily risk of VTE during the postpartum period increases by up to 35-fold in comparison with non-pregnant women of the same age.

Seventy-four to ninety percent of DVT occur in the left leg[2,3,5] with the majority occurring in the very proximal deep ilio-femoral vein[7] with greater likelihood of embolization. Coriu et al.[6] attributes this location of thrombotic events to be as a result of the right iliac artery compressing the left iliac vein, as well as that of the inferior vena cava by the gravid uterus resulting in increased venous stasis in the proximal left leg.

1.1 Pathophysiology

Pregnancy is associated with a hypercoagulable state as a result of changes that can be explained by Virchow's Triad namely, changes in blood constituents, venous stasis and vascular endothelial intimal damage[8,9].

Possible aetiological factors are complex and include mechanical factors, such as obstruction by the fetal head and gravid uterus on the pelvic veins[9,10], causing a reduction in venous blood velocity as well as an increase in the blood pressure of lower limb veins[1]. Gyselaers[11] describes three fundamental aspects in venous haemodynamic function during normal pregnancy that differs from non-pregnant conditions, namely: (a) vascular tone is reduced, with an increased venous capacitance function, (b) the venous compartment participates in the gestational body water volume expansion in order to maintain optimal cardiac output, and (c) high intra-abdominal pressures causes increased transmural venous pressure. The above contribute to reduced venous blood flow with the venous system functioning closer to its maximum limits during pregnancy.

In pregnancy, nearly all procoagulants are increased, creating a state in which equilibrium is shifted toward coagulation[9,12]. Struble et al.[9] believes this to be an evolutionary adaptation whereby the pregnant woman facing the trauma of childbirth may be equipped to survive. Coriu et al. and Shagana et al.[6,12] specify increases in factors VII, VIII, IX, X, XII, von Willebrand Factor and fibrinogen as well as reductions in fibrinolytic activity with decreased levels of anticoagulants Antithrombin and Proteins C and S.

Endothelial injury or activation as a result of inflammatory stimuli or hypoxia that may occur in early pregnancy leads to the activation of circulating leukocytes and induction

of expression of tissue factor which adjusts the intimal surface to that of a prothrombotic state. In addition, hormonal changes in estrogen levels augment the above-mentioned increases in procoagulants, further predisposing pregnant women to clot formation[9].

1.2 Pre-eclampsia

Pre-eclampsia is characterised by new onset hypertension after 20 weeks gestation, in association with organ dysfunction such as renal and liver dysfunction, clotting disorders, fetal affectation and neurological dysfunction[11,13]. This condition complicates up to seven percent of pregnancies and is associated with substantial morbidity and mortality[13]. Egan et al.[13] suggest that the risk of VTE in women with pre-eclampsia may be up to 5-fold greater than that of the general pregnant population and attribute this increased risk to mechanisms of an overall pro-inflammatory state as well as endothelial, platelet and coagulation activation with release of procoagulant neutrophil extracellular traps (NETs).

1.3 Imaging and Diagnosis

Venous compression ultrasonography has become the imaging test of choice for diagnosis of DVT in the lower extremities[5,7,8] with 97 percent sensitivity for detecting DVT in the femoral and popliteal veins[8]. It is however less sensitive for the detection of isolated DVT in the distal calf veins. Physiological changes associated with pregnancy may affect blood flow patterns and normal compressibility of the proximal veins and therefore influence the diagnostic accuracy of compression ultrasonography. Furthermore, the intrapelvic location of the more proximal veins are not compressible due to their location[7]. Doppler imaging, including colour flow, may be recommended as an additional tool to assess the proximal iliac veins and

accurately identify vessels and confirm the compressibility of a particular segment[7,8]. Typical ultrasonographic findings associated with DVT include: reduced compressibility of the vein wall due to rigidity as well as a lack of or reduced spontaneous blood flow at the point of, and distal to, the occlusion[1].

Studies have been performed to assess the changes in lower limb veins associated with pregnancy such as by Rabhi et al.[10] who non-invasively ascertained the functions of lower limb veins in women with normal pregnancies, in all three trimesters and puerperium, to assess the changes in wall compliance, spontaneous blood echogenicity and diameter. They noted that forty-three percent of their participants reported complaints of venous insufficiency, namely lower leg pain, oedema, cramps, paraesthesia. They also noted an increased diameter of the great saphenous veins, with associated valve incompetence which continued after delivery. Their postulation was that these pregnancy-related changes may produce permanent anatomic lesions. They also commented on blood flow echogenicity and stasis relating to red cell aggregation with rouleaux formation. They highlighted, however, that this should not be mistaken for venous thrombosis as it appears to be a normal finding in pregnancy.

In comparison, Palmgren and Kirkinen[1] evaluated the physiological changes in the venous circulation of the lower extremities during pregnancy to assemble normal velocity values of the venous flow in this area. They examined the effects of the Valsalva maneuver on the valvular system and vein wall distensibility. They found typical decreases in blood flow velocities during pregnancy that normalised after delivery. Sparey et al.[14] used colour flow duplex scanning to assess the consequences of pregnancy on women with established varicose veins. They assessed the changes in reflux and venous diameter in women in all three trimesters and concluded that the effects of pregnancy worsen pre-existing varicose veins. They noted a left sided

predominance with a tendency for all lower limb veins to dilate, reaching a maximum at term, as well as an increased reflux velocity with advancing gestation, reaching a peak at 26 weeks.

1.4 Management

It is well established that pregnancy is associated with diminished blood flow in the lower limbs, with increased risk of the development of VTE. The question that remains controversial is whether to use prophylactic anticoagulants during pregnancy and the puerperium to prevent the development of VTE and its severe consequences. This is a challenging topic due to the potential for complications to both the fetus and mother. The decision to start anticoagulation prophylaxis during pregnancy is based on determining the risk to benefit ratio and finding a balance between the anticipated risk of VTE, the reduction in risk if given prophylaxis, as well as the burden associated with the use of anticoagulants[4].

Risk factors to be considered include age greater than 35 years, increased body mass index (BMI), grand multiparity, personal or family history of VTE, immobility for more than one week, dehydration, hyperemesis, smoking, surgery, trauma, severe varicose veins and medical conditions such as known thrombophilia, pre-eclampsia, congestive cardiac failure, nephrotic syndrome, diabetes mellitus and severe infection[4,5,15]. A prior history of thrombosis is the most important individual risk factor for pregnancy-associated VTE, with a reported recurrence ranging from 2.4 to 6 percent[4].

Bain et al.[16] conducted a Cochrane systematic review of thromboprophylaxis in pregnancy and the early postnatal period. They concluded, after examining 16 randomized trials involving 2592 women, that current information is insufficient to make firm recommendations for prophylaxis and suggest a larger scale study to be

performed. Furthermore, there is incomplete agreement between the international guidelines made by the various associations, which is explained in more detail in appendix A[4].

South African guidelines for thromboprophylaxis in pregnant patients by Schapkaitz et al.[17] suggest the use of an anticoagulant that does not cross the placenta and can be easily reversed, preferably a low molecular weight heparin (LMWH). It should be initiated early in the antepartum period with recommended fixed doses of either dalteparin 5 000, nadroparin 2 850 units or enoxaparin 40 mg daily[17]. Schapkaitz et al.[17], also recommend weekly monitoring of platelets after initiation, as well as dose adjustments to achieve a target anti-Xa level of 0.3 - 0.5 units/ml. Postpartum thromboprophylaxis should be continued for varying durations depending on the level of risk identified. All women prior to pregnancy should therefore undergo an individualized risk evaluation for VTE, and again when pregnancy is confirmed, also should new clinical situations arise during the pregnancy. Furthermore, should patients present with symptoms of the development of VTE, Doppler studies may assist with confirming the diagnosis and need for anticoagulation.[4]

Further research is necessary to establish normal parameters in lower limb venous function and blood flow during pregnancy in order to assist with risk stratification and identification of patients that may benefit from prophylactic anticoagulation. Additionally, a comparison between patients with normal anatomy and those with anticipated vascular dysfunction may assist with identifying patients at risk of developing VTE disease in pregnancy.

2. STUDY OBJECTIVES

The aim of the study is to describe and compare lower extremity venous Doppler flow in normal pregnancies and women with pre-eclampsia in the third trimester. The objectives are the following:

6. To describe the demographics and clinical characteristics of patients undergoing doppler ultrasound of the lower extremities.
    a. And further describe mode of delivery, gestational age at delivery as well as describe short-term outcomes relating to birth APGAR scores and weight.
7. To compare spontaneous blood flow echogenicity of lower extremity veins in normal pregnancies in the third trimester with that of pre-eclamptic women, by using a grading system.
8. To compare venous doppler wave forms of lower extremity veins in normal pregnancies in the third trimester with that of pre-eclamptic women, to assess patency of the vessels.
9. To compare the compressibility of lower extremity vein walls in normal pregnancies in the third trimester with that of pre-eclamptic women.
10. To compare diameters of lower extremity veins in normal pregnancies in the third trimester with those of pre-eclamptic women.

3. METHODOLOGY

3.1 Study design and population

This study will be in the form of a prospective case control study and record review. The stratified sampling technique will be used to select patients presenting to Rahima Moosa Mother and Child Hospital. Patients will be approached at the convenience of the researcher or her supervisors. A screening log (Appendix B) will be kept with the

reason for exclusion. Patients will be recruited from the antenatal clinic and the antenatal wards. If they are eligible, their information will be collected, and the sonar findings will be recorded. They will be selected from the time of ethical clearance to the point of obtaining a sample size of approximately 100 patients. This time period is expected to be approximately three months. The sample size will incorporate two groups with 50 individuals allocated to the group with pre-eclampsia and 50 to the control group without preeclampsia.

Inclusion Criteria

1. Singleton pregnancy
2. Gestational age of between 27 and 41 completed weeks determined by either:
    a. early ultrasound (<14 weeks)
    b. last menstrual period with a history of regular menstrual cycles
3. No observed malformation of the fetus

1. Pre-eclamptic group – diagnosis as per ISSHP guidelines[18]:
    a. Hypertension as evidenced by blood pressure (BP) greater than or equal to 140 mmHg systolic or 90 mmHg diastolic, on two separate occasions more than 4 hours apart; Or only one elevated BP of greater than or equal to 160 mmHg systolic or greater than or equal to 110 mmHg diastolic.
    b. Diagnosis after 20 weeks gestation in a woman with previously normal BP.
    c. In combination with one or more of the following new onset conditions:
        i. Proteinuria – excretion of 300 mg or more protein on 24-hour urine collection; or spot urine protein/creatinine ratio of greater than 0.3 g/dl; or 2+ proteins on a urine dipstick.
        ii. Renal Insufficiency – serum creatinine ≥ 90 umol/l.

iii. Liver involvement – elevated transaminases at least twice the upper limit of normal, severe right upper quadrant or epigastric pain.

iv. Neurological complications - eclampsia, altered mental status, blindness, stroke, hyperreflexia when accompanied by clonus or severe headaches, persistent visual scotomata.

v. Haematological complications - thrombocytopenia, disseminated intravascular coagulopathy, haemolysis.

vi. Uteroplacental dysfunction - fetal growth restriction

Exclusion Criteria

1. Cigarette smoking history
2. Previous venous thromboembolism
3. History of the following pre-pregnancy medical conditions that are known to impact vascular function:
    a. Diabetes Mellitus
    b. Hypertension
    c. Auto-immune conditions
    d. Cardiac disease
    e. HIV positive

3.2 Data Collection

After counselling and signing informed consent (Appendix C), questionnaires (Appendix D) will be completed by both groups, in the form of an interview which will take approximately 15 minutes. The following information will be obtained from their antenatal care (ANC) patient records: age, parity, height and weight at ANC booking, previous deliveries and medical conditions. Patients will be given the opportunity to decide whether they would like to participate in the study or decline participation.

Positioning of the patient for the purposes of doppler examination of the lower extremities will include tilting the patient in reverse Trendelenburg position to induce venous distension and minimise compression of the inferior vena cava[14]. The subject will lay on her left side with the left lower limb straight, the right side will be elevated obliquely by 20 degrees with the right lower limb supported by a soft pillow to keep the knee flexed to 60 degrees, and the upper body will be elevated by 15 degrees[1,10]. The purpose of this positioning is to ensure measurements will be made at the same level as the right atrium of the heart.

Each patient will be examined once using a Philips EPIQ 5 Colour Doppler Ultrasound System with a high frequency L12-3, 50 Hz linear array probe and 50 Hz Doppler with the option of steering the colour box to an acceptable angle for optimal Doppler shift recording. The ultrasound procedure will take approximately 30 minutes and will be performed by the same trained and qualified ultrasonographer, who is the same person to perform examinations on patients who are suspected of having a DVT. Should a DVT be diagnosed during examination, the required steps will be taken to ensure that the patient is appropriately treated and followed up.

The measurements of vein diameter, compressibility as well as waveform and spontaneous blood flow echogenicity will be assessed after ten minutes rest on both left and right lower limbs. Each leg will be scanned from the saphenofemoral junction to the ankle at the following points, with minimal pressure applied to the skin to avoid venous compression[14]:

v. Common femoral vein (CFV), 10cm below saphenofemoral junction.
vi. Superficial femoral vein (SFV), 5cm below the junction forming the CFV.
vii. Popliteal vein (POP), at the level of the skin crease in the popliteal fossa.
viii. Short saphenous vein (SSV), 5cm below its junction with the popliteal vein.

Data will be transcribed onto an ultrasound data collection sheet (Appendix E).

1. Spontaneous blood flow echogenicity will be graded as follows[10]:

    Grade 0 - Anechoic (absent)

    Grade 1 - Barely visible echoes

    Grade 2 - Clearly visible echoes whose intensity remains lower than that of surrounding tissues

    Grade 3 - Blood flow echogenicity equal to or greater than that of surrounding tissues (Hyperechoic)

2. Abnormal waveforms infer a possible proximal venous occlusion. Waveforms will be assessed using pulsed-wave Doppler, following augmentation by squeezing the extremity distally[11] and are categorised as follows:
    a. Triphasic - forward flow in systole; reverse flow in late systole/early diastole; forward flow in late diastole.
    b. Biphasic - reverse flow in diastole; steady positive flow in the diastole, or forward flow in systole.
    c. Monophasic - single phase with slow flow (acceleration/deceleration).
    d. Flat - Non-pulsatile, abnormal waveform.
3. Compressibility of veins will be assessed and graded as either compressible (‘yes’), incompressible (‘No’) or partially compressible, to assess the formation of thrombi in the veins[8].
4. The diameters will be measured, in millimetres, at above sites[10].

3.3 Statistical analysis

Data collected will be uploaded onto the REDCap program. Statistical evaluation will be carried out using the Statistica program with data analysed as follows:

a. Numerical data – age, gestational age, BMI, diameter of vessel walls, birth APGAR score and birth weight. Testing for normality will be done using Shapiro-Wilks test; and will be expressed depending on distribution as follows:
    i. Parametric - Mean +/-Standard deviation, using box and whisker plots.
    ii. Non-Parametric - Median, interquartile range.
b. Categorical data – Mode of delivery, HIV status, grading of spontaneous blood flow echogenicity, vein wall compressibility and waveforms will be expressed as percentages and frequencies using tables, bar and pie charts.

Mann-Whitney U test, unpaired Student's t-test and Chi-square test will be used to compare the two groups using a p-value of < 0.05 as the level of significance.

3.4 Limitations

The sonographer will not be blinded to the condition of the patients as she will have access to the files. She will therefore be aware of the group to which each person is allocated. Furthermore, a larger sample size will generate a study with greater statistical power.

4. ETHICAL CONSIDERATIONS

Ethical clearance will be requested from the University of the Witwatersrand's Human Research Ethics Committee. As this will be a prospective study, patients will need to provide informed consent prior to participating in the study. They will be informed of the procedure to be undertaken, and that it is not invasive nor harmful to themselves or their baby. They will have the right to decline participation in the study or choose to have their details removed from the study should they change their minds.

Patients' identities and details will be kept strictly confidential by ensuring that documentation refers to their initials and hospital numbers. For record keeping

purposes, each participant will be allocated a study number which will be used to form the main data set, and only be available to the researcher and supervisors.

Permission to conduct the study has been approved by the CEO at Rahima Moosa Mother and Child Hospital. The study will be registered with the National Health Research Database.

5. FUNDING

There are no costs that will be incurred by the hospital or university. All printing, transport and administration costs will be borne by the researcher, as follows:

Item	**Description**	**Units**	**Unit cost**	**Price**
Consumables	Printing/Binding	800	R0.50	R400
	Each of the 100 participants would require a printout of at least four sheets of paper for completion of informed consent, questionnaire and data collection sheet. Additionally, printing and multiple copies of completed protocol and final report.			
	Stickers	100	R2.00	R200
	Each participant will have a sticker placed on their file indicating their participation in the study.			
Travelling	Maintenance	192 km	R4.75/km	R912
	Approximately 10 trips to RMMCH at 19.2 km per trip, according to AA maintenance rates per km			
	Fuel	192 km	R15.92/litre	R195
	(Total Distance/100) x average fuel consumption (6.4 L) x cost of fuel/L			
			TOTAL	**R1707**

6. DURATION OF STUDY

	2019			2020								
	JUN	**JUL**	**SEP**	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**	**AUG**	**SEP**	**OCT**
Protocol Submission	**26/6**											
Protocol Assessment		**10/7**										
Ethics Application			**6/9**									
Data Collection				**X**	**X**	**X**	**X**					
Data Analysis								**X**	**X**			
Report Write-up										**X**	**X**	**X**

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Appendix B: Screening log of patients

Will be done by supervisors when seeing patients in ANC clinic and fetal medicine department

NO.	DATE	ELIGIBLE		CONSENT		EXCLUSION CRITERIA
		◻ Yes	◻ No	◻ Yes ◻ No ◻ Declined Reason for declining ◻ Time ◻ Not interested		◻ Smoking ◻ VTE ◻ Diabetic ◻ Cardiac ◻ Auto immune ◻ HIV positive ◻ Hypertensive

Appendix C: Informed consent form

STUDY INFORMATION SHEET

Research Title: Lower extremity venous doppler flow in normal pregnancies and women with pre-eclampsia in the third trimester
(Prior to title adjustment)

Principal Investigator: Dr RB Fortuin, Registrar in Obstetrics & Gynaecology
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Dr Amy Wise, Fetal Medicine Specialist
Rahima Moosa Mother and Child Hospital

We are asking / inviting you to take part in a research study. Research is a process used in seeking new knowledge. In this study we want to learn about the veins in the lower legs of pregnant women. This is important because it may assist us with identifying patients who are at risk of developing clots, which is a very serious condition.

1. What will the study entail?

You will be asked to complete a questionnaire to provide information about the following: your age, previous pregnancies and deliveries, last menstrual period, height and weight, as well as medical conditions. You will be placed in one of two groups, depending on whether you have been diagnosed with pre-eclampsia in the pregnancy.

You will not be able to participate in the study if you have a history of smoking cigarettes, have had a previous venous thromboembolism (clot in the veins), or have any of the following medical conditions that may affect the quality of your veins:

- Diabetes Mellitus
- Hypertension
- Auto-immune conditions
- Cardiac disease
- HIV

2. What other things should you know about this research study?

This study involves performing an ultrasound on your legs in order to assess the veins. Participation in this study will take approximately 30 minutes of your time, on only one occasion. There are no anticipated risks or discomforts. There are no direct benefits of participating. There is no cost involved. Should a clot in the leg be identified, it will be managed accordingly.

Your participation in this study is completely voluntary. Should you decide to discontinue participation you may do so without penalty.

Your privacy will be protected by ensuring that only the research team will know your identity and that you are in the research study. The data may be used for future research and publications however, you will remain anonymous.

Should you have any further questions, please feel free to contact the study's principle investigator, as mentioned above.

INFORMED CONSENT

Research Title: Lower extremity venous doppler flow in normal pregnancies and women with pre-eclampsia in the third trimester

(Prior to title adjustment)

I, the undersigned, confirm that (please tick box as appropriate):

1.	I have read and understood the information about the project, which has been explained to me in detail as provided in the Information Sheet	□
2.	I have been given the opportunity to ask questions about the project and my participation.	□
3.	I voluntarily agree to participate in the project.	□
4.	I understand I can withdraw at any time without giving reasons and that I will not be penalised for withdrawing nor will I be questioned on why I have withdrawn.	□
5.	The procedures regarding confidentiality have been clearly explained (e.g. use of names, pseudonyms, anonymisation of data, etc.) to me.	□
6.	The use of the data in research, publications, sharing and archiving has been explained to me.	□
7.	I, along with the Researcher, agree to sign and date this informed consent form.	□

Participant:

_____	_____	_____
Name of Participant	Signature	Date

Researcher:

_____	_____	_____
Name of Researcher	Signature	Date

Appendix D: Antenatal Questionnaire

LOWER EXTREMITY VENOUS DOPPLER FLOW IN NORMAL PREGNANCIES AND WOMEN WITH PRE-ECLAMPSIA IN THE THIRD TRIMESTER

(Prior to title adjustment)

QUESTIONNAIRE

Pre-eclamptic: **Yes/No**

Name: Surname:

Date of birth: Hospital Number:

OBSTETRIC HISTORY

Para: Gravida: @ Gestational age:

YEAR	C/S vs NVD	ALIVE	GEST. AGE	COMPLICATIONS

EDD: by Dates / EUS

LNMP: Sure / Unsure

MEDICAL HISTORY

Medical Conditions:

HIV status: Reactive / Non-reactive

Smoker: Yes / No / Quitter

Medication:

Weight (first recorded): Height:

BMI:

Mode of delivery: C-section / NVD

Date of delivery:

Gestational age at delivery:

Appendix E: Ultrasound data collection sheet

LOWER EXTREMITY VENOUS DOPPLER FLOW IN NORMAL PREGNANCIES AND WOMEN WITH PRE-ECLAMPSIA IN THE THIRD TRIMESTER

(Prior to title adjustment)

DOPPLER ULTRASOUND – LOWER EXTREMITIES

Pre-eclamptic: **Yes / No**

Name: Surname:

Hospital Number: Date:

	Common Femoral		Femoral		Popliteal		Small Saphenous	
	L	R	L	R	L	R	L	R
Blood Flow (Patency)								
Waveform (Phasicity)								
Compressible (Thrombus)								
Diameter								

Key**:**

Blood Flow Echogenicity	
Grade 0	Anechoic (absent)
Grade 1	Barely visible echoes
Grade 2	Clearly visible echoes
Grade 3	Hyperechoic

Waveform	
Triphasic	T
Biphasic	B
Monophasic	M
Flat	F

Compressibility
Yes
No
Partial

Comments:

Appendix F: Guidelines on choice of anticoagulant during pregnancy[4]

American College of Obstetricians and Gynecologists (ACOG)	**Society of Obstetricians and Gynaecologists of Canada (SOGC)**	**Royal College of Obstetricians and Gynaecologists (RCOG)**	**Australia/ New Zealand**	**American College of Chest Physicians (ACCP)**
Heparin compounds are the preferred anticoagulant during pregnancy **(Level B)**	LMWH is the preferred pharmacologic agent over UFH for treatment of VTE during pregnancy **(II-2A)** LMWH is the preferred pharmacologic agent over UFH for antepartum thromboprophylaxis **(III-A)** LMWH is the preferred pharmacologic agent over UFH for postpartum thromboprophylaxis **(IIIA)**	LMWH is the preferred anticoagulant for treatment of acute VTE during pregnancy **(B)** LMWHs are the agents of choice for antenatal and postnatal thromboprophylaxis **(A)** Because of their adverse effects on the fetus, vitamin K antagonists should not be used for antenatal VTE treatment **(C)** Women receiving long-term vitamin K	Women with VTE in pregnancy should not be treated with vitamin K antagonists, such as warfarin **(Consensus Level 1)**	For pregnant patients, recommend LMWH for prevention and treatment of VTE, instead of UFH **(Grade 1B)** For pregnant women, recommend avoiding the use of oral direct thrombin and factor Xa inhibitors **(Grade 1C)** For women requiring long-term vitamin K antagonists who are attempting pregnancy and are

	Vitamin K antagonists should only be considered for treatment of VTE in exceptional circumstances **(II-2A)** Recommend against the use of oral Xa inhibitors and oral direct thrombin inhibitors **(III-D)**	antagonist therapy should be counselled about the risks of vitamin K antagonists to the fetus and advised to stop these medications and change to LMWH as soon as pregnancy is confirmed (ideally within 2 weeks of the missed period and before the 6th week of pregnancy) **(no grade)** Oral thrombin and Xa inhibitors should be avoided in pregnant women **(no grade)**		candidates for LMWH substitution, suggest performing frequent pregnancy tests and substituting LMWH for vitamin K antagonists when pregnancy is achieved rather than switching to LMWH while attempting pregnancy **(Grade 2C)**

Appendix G: Ethical Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Rori Fortuin

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190964

NAME: (Principal Investigator)	Dr Rori Fortuin
DEPARTMENT:	School of Clinical Medicine Obstetrics and Gynaecology Rahima Moosa Mother and Child Hospital
PROJECT TITLE:	Lower extremity venous doppler flow in pregnancies with and without pre-eclampsia in the third trimester
DATE CONSIDERED:	27/09/2019
DECISION:	Approved unconditionally
CONDITIONS:	Title change
SUPERVISOR:	Prof H. Lombaard and Dr A. Wise
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/01/2020 (Initial approval); 10/06/2021 (Title change)

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **September** and will therefore be due in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

11/06/2021
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix H: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Rori Fortuin (Student number: 550531) am a student registered for the degree of Master of Medicine in the academic year 2022.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
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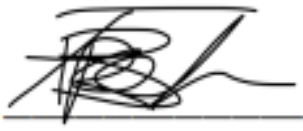
Signature: 

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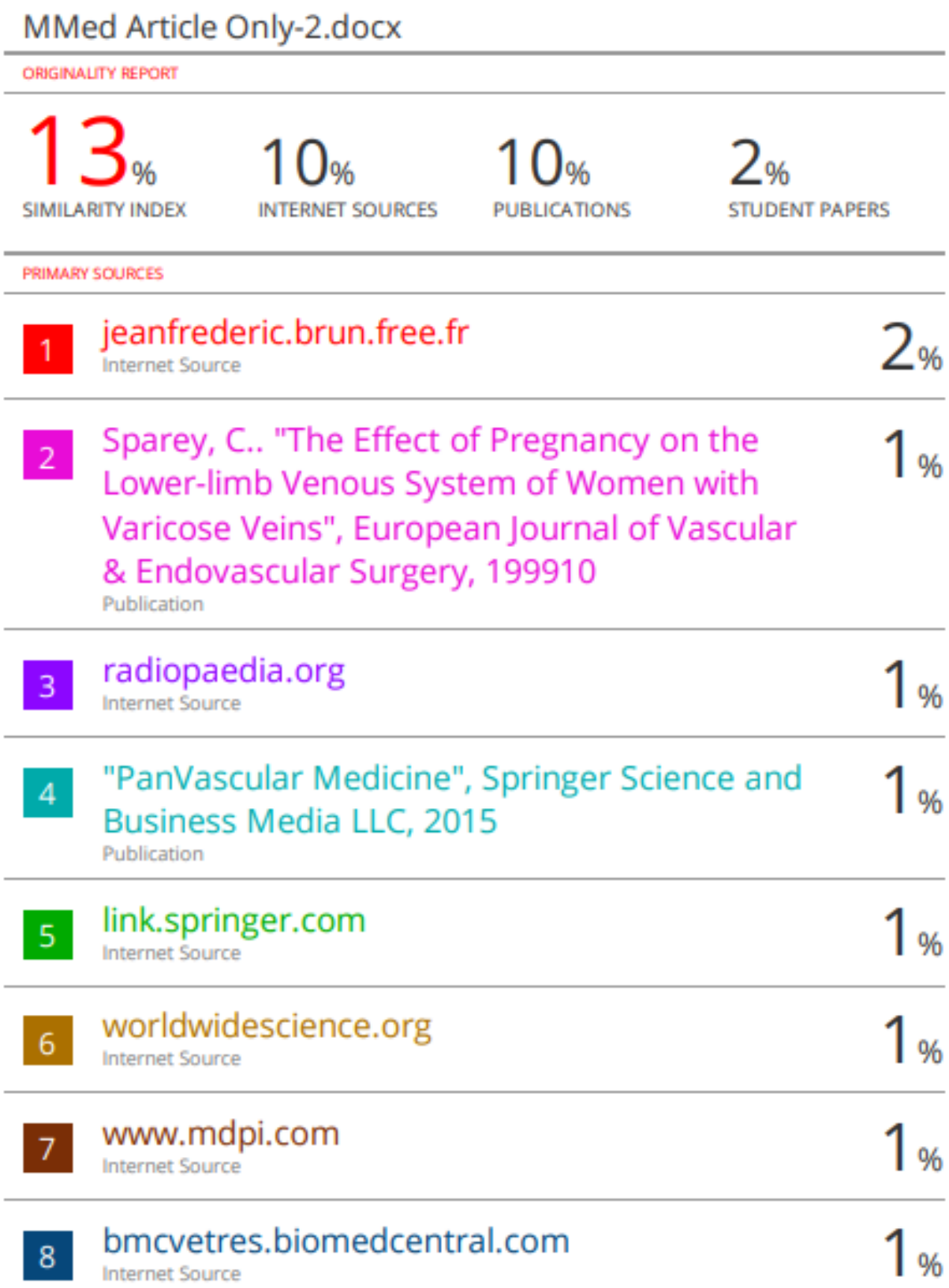

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Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

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An International Journal of Women's Cardiovascular Health

AUTHOR INFORMATION PACK

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We publish articles pertaining to human and animal **blood pressure** during **gestation**, **hypertension** during gestation including physiology of circulatory control, pathophysiology, methodology, therapy or any other material relevant to the relationship between elevated blood pressure and pregnancy. The subtitle reflects the wider aspects of studying hypertension in pregnancy thus we also publish articles on in utero programming, nutrition, long term effects of hypertension in pregnancy on cardiovascular health and other research that helps our understanding of the etiology or consequences of hypertension in pregnancy. Case reports are not published unless of exceptional/ outstanding importance to the field.

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Reference to a book:
[3] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.
Reference to a chapter in an edited book:
[4] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304.
Reference to a website:
[5] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13 March 2003).
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Appendix K: Highlights

- Pregnancy is associated with increased incidence of venous thromboembolism
- There is a 5-fold greater risk of venous thromboembolism in pre-eclamptics
- The blood vessel lumen is usually free of internal echoes during ultrasonography
- Red cell aggregation and low blood velocity is a marker of thromboembolic risk
- Spontaneous blood flow echogenicity grade increases as the pregnancy progresses