Tendency For Varicose Vein Formation In Pregnancy

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Abstract

Varicoses remains an important issue related to obstetrics since pregnancy is one of the leading factors causing varicoses in women. Physiological complex and hormonal changes in pregnancy cause veins distension followed by valves dysfunction, endothelial injury marked by the increase of soluble Vascular Cell Adhesion Molecules-1 (VCAM-1) in the circulation, and supported by femoral and great saphenous veins dilatation and reflux in the saphenous-femoral junction. The objectives of this study are to examine the possibility to use measurements of soluble VCAM-1, levels of platelet activations, alterations in veins structure and function of lower limbs veins as early detection methods to reduce the risk of varicoses in primigravida wearing elastic stockings with mechanical compression. A prospective study was performed in a randomized single blinded trial with analysis of variance and repeated measures. The study was done at The Obstetric and Gynaecology Department Immanuel Hospital Bandung, with subjects obtained from the Obstetrics outpatient clinic and Astana Anyar Maternity Hospital Bandung during the period of May 2005 to March 2006. This study consisted of a population of 66 primigravida randomly allocated in to 2 groups, 34 women in control group and 32 women in study group. Women in the study group were instructed to wear elastic stockings, while the control group was not. Measurements of VCAM-1 were performed using ELISA (Enzyme-Linked Immunosorbent Assay). Measurements of veins dilatation were carried out using a Color Duplex Ultrasound. Levels of platelet aggregation were measured with a platelet aggregometer. Examination of 12 weeks and 34 weeks gestational age showed the average of VCAM-1 concentrations in the control group were increased as high as 194,6 ± 113,6 ng/ml compared to 82,5 ± 65,3 ng/ml in the study group. The study group also has less dilatated left femoral veins and great saphenouns veins (subsequently 0,83 ± 0,07 cm and 0,83 ± 0,07 cm) compared to control group (subsequently 1,02 ± 0,35 cm and 1,01 ± 0,35 cm).Tthe incidence of reflux was found only in the study group at sapheno-femoral junction in 6 of 34 women. Alterations in platelets aggregations and count were found not statistically significant in both groups, indicating the process occurred locally and had a minimal effect in the alterations of platelets activation profile.

In conclusions, our findings suggest that, the pathogenesis of varicoses started from excessive increase in diameter of lower limbs and pelvic veins, resulting the endothelial injury and followed by the increase of soluble VCAM-1 expression. Mechanical compression provide protective effect from the development of varicoses shown by the reduced VCAM-1 expression, reduced incidence in developing reflux in blood flow in saphenous-femoral junction, in addition to minimal dilatation of the lower limbs and pelvic veins.

Keywords: varicoses; pregnancy; endothelial injury; VCAM-1; saphenous-femoral junction; reflux; mechanical compression

Introduction

Varicoses becoming a more important issue lately since they cause many aesthetic problems and most importantly causing legs discomfort. A serious complication may also follow untreated varicoses such as thrombosis. Varicoses occur as a result of veins

distention marked with the appearance of enlarged and elongated veins[1,2]. There are several predisposing factors that may contribute to the occurrence of varicoses in females. These factors are including genetic factors, old age, the usage of hormonal contraception, obesity, activities which require a long time to stand still, and most importantly is pregnancy[2].

Although varicoses is not included in the three main causes of Maternal Death, varicoses remains an important aspect that reduces women's productivity and life quality. Varicoses cause leg discomforts, pain, and aesthetics problems which may require high cost treatments including vascular surgery therapies[3-5].

Studies in determining the varicoses prevalence and its complications have never been conducted in Indonesia. However, there was found a difference in varicoses prevalence between white females (49%) compared to Asian females (36%) which lead to an assumption that death as a complication of varicoses is also lower in Asia than those in Western countries[6]. Based on studies carried out in Europe it was shown that during the first pregnancy (primigravida) the incidence of varicoses occurrence was as high as 30-35%. This relatively high number also contributes to the higher risk of developing varicoses in the subsequent pregnancy or even after menopause[6-8].

Materials And Methods

This study was performed in a randomized single blinded trial with analysis of variance and repeated measures.

Results and Discussions

This study consisted of a population of 66 primigravida randomly allocated in to 2 groups, 34 women in control group and 32 women in study group. Women in the study group were instructed to wear elastic stockings, while the control group was not.

As shown on table 1, based on the age, body mass index, VCAM-1 levels, and platelets aggregation profiles there were no significant differences among non-pregnant and the primigravida on the first 12 weeks of pregnancy. Therefore these data also showed only minimal changes occuring during the first 12 weeks of pregnancy and thus eliminate the possibility of results bias.

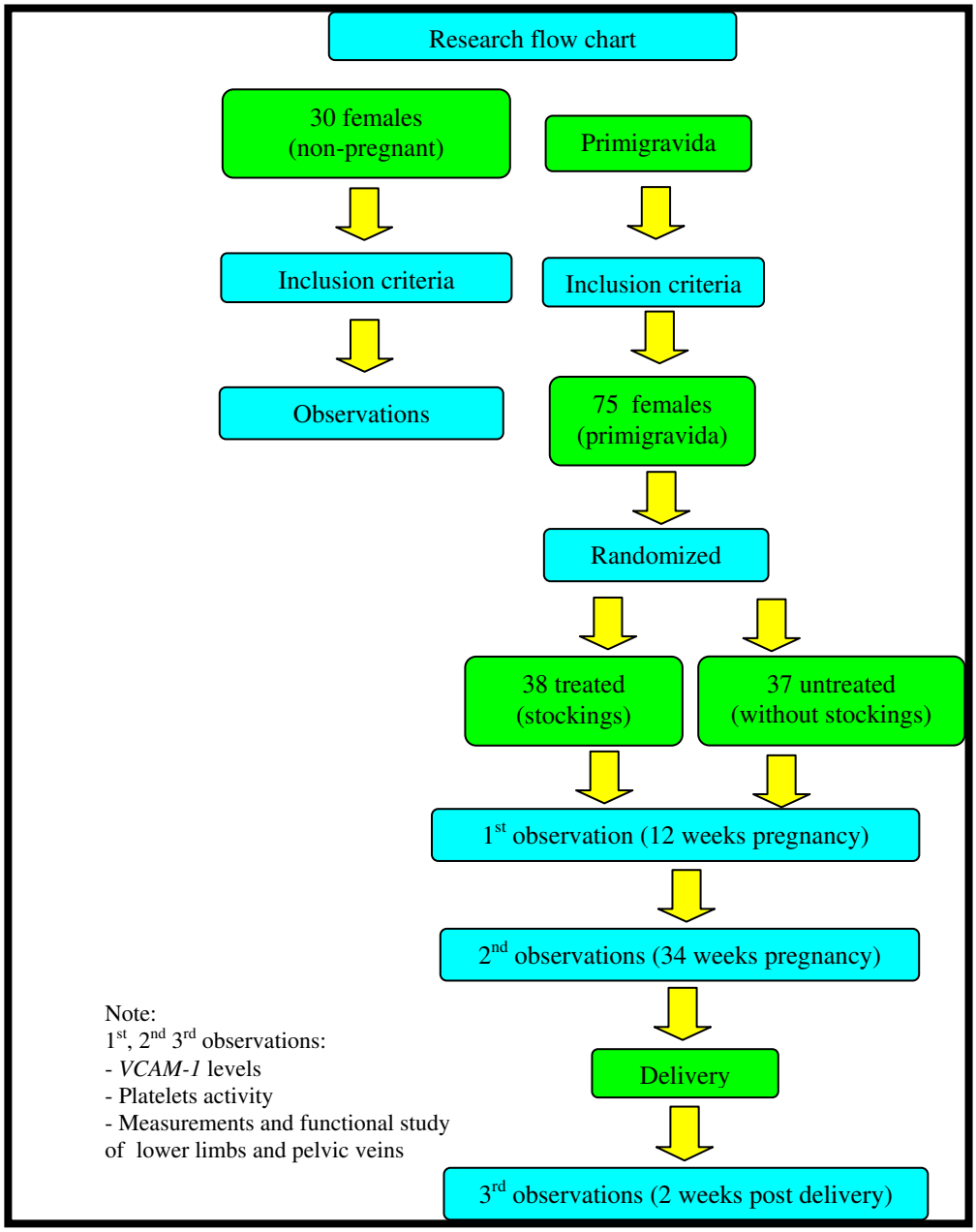
Research flow chart
30 females (non-pregnant)
Primigravida
Inclusion criteria
Inclusion criteria
Observations
75 females (primigravida)
Randomized
38 treated (stockings)
37 untreated (without stockings)
1st observation (12 weeks pregnancy)
2nd observations (34 weeks pregnancy)
Delivery
3rd observations (2 weeks post delivery)
Note:
1st, 2nd 3rd observations:
- VCAM-1 levels
- Platelets activity
- Measurements and functional study of lower limbs and pelvic veins

Table 1 Comparisons of individual characteristics (Age, Body Mass Index), VCAM-1 levels, and platelets aggregations among the three groups

No	*Variables*	*Groups*			*Significance*
		Treated (n=32)	Untreated (n=34)	Non-pregnant (n=30)	
1.	Age (years)				
	x (SD)	25.0 (3.3)	25.0 (3.7)	25.7 (2.3)	F=0.501
	Range	20-30	20-30	20-30	*p*=0.685
2.	Body Mass Index (kg/m^2)				
	x (SD)	22.7 (2.2)	23.0 (1.7)	22.6 (2.2)	F=0.399
	Range	19.8-26	19.8-26	19.8-26	*p*=0.672
3.	*VCAM-1* (ng/ml)				
	x (SD)	357.3 (162.1)	361.4 (113.5)	362.2 (153.7)	X^2_{K-W}=0.176
	Median	341.6	329	341.6	*p*=0.916
	Range	102.8-841.4	202-540.2	102.8-841.4	
4.	Platelets aggregations				
	Hiper	9 (28.1)	12 (35.3)	10 (33.3)	X^2=0.553
	Hipo	3 (9.4)	3 (8.8)	2 (6.7)	*p*=0.968
	Normo	20 (62.5)	19 (55.9)	18 (60.0)	
5.	Platelets aggregations (%)				
	x (SD)	63.8 (8.2)	64.2 (7.3)	64.4 (7.6)	X^2_{K-W}=0.231
	Median	65.8	65.3	66	*p*=0.891
	Range	45.3-78.2	47.3-75.3	45.3-76.3	

Note:
F = variants analysis
X^2_{K-W} = chi square test (Kruskal – Wallis)

Table 2. Comparisons of lower limbs and pelvic veins diameters during the 1st 12 weeks of pregnancy

No.	*Variables*	*Groups*			X^2_{K-W}	*P value*
		Treated (n=32)	Untreated (n=34)	Non-pregnant (n=30)		
1.	Left femoral veins				0.745	0.689
	x (SD)	0.80 (0.07)	0.81 (0.06)	0.81 (0.07)		
	Median	0.79	0.79	0.82		
	Range	0.64-0.92	0.64-0.92	0.64-0.92		
2.	Right femoral veins				5.10	0.078
	x (SD)	0.79 (0.07)	0.76 (0.07)	0.81 (0.07)		
	Median	0.78	0.76	0.80		
	Range	0.64-0.92	0.60-0.92	0.64-0.92		
3.	Left greater saphenous veins				1.148	0.563
	x (SD)	0.80 (0.07)	0.81 (0.07)	0.82 (0.07)		
	Median	0.80	0.78	0.83		
	Range	0.64-0.93	0.64-0.95	0.64-0.92		
4.	Right greater saphenous veins				4.844	0.089
	x (SD)	0.79 (0.07)	0.77 (0.06)	0.79 (0.07)		
	Median	0.78	0.76	0.78		
	Range	0.64-0.92	0.65-0.93	0.64-0.92		
5.	Left popliteal veins				1.006	0.605
	x (SD)	0.80 (0.07)	0.80 (0.06)	0.81 (0.07)		
	Median	0.79	0.78	0.79		
	Range	0.62-0.92	0.64-0.92	0.62-0.94		
6.	Right popliteal veins				3.045	0.218
	x (SD)	0.79 (0.07)	0.77 (0.06)	0.79 (0.07)		
	Median	0.78	0.76	0.78		
	Range	0.64-0.92	0.60-0.92	0.64-0.92		
7.	Left external iliac veins				0.197	0.906
	x (SD)	0.80 (0.07)	0.80 (0.07)	0.80 (0.07)		
	Median	0.79	0.79	0.79		
	Range	0.64-0.92	0.64-0.92	0.64-0.93		
8.	Right external iliac veins				4.744	0.093
	x (SD)	0.79 (0.07)	0.80 (0.07)	0.80 (0.07)		
	Median	0.78	0.76	0.78		
	Range	0.64-0.92	0.60-0.92	0.63-0.92		

Note: Measurements were in centimetres
X^2_{K-W} = chi square test (Kruskal – Wallis)

Table 3. *VCAM-1* levels between treated and untreated groups

No	*Variables*	*Groups*		Z_{M-W}	*P value*
		Treated (n=32)	Untreated (n=34)		
1.	*VCAM-1* (I)				
	x (SD)	357.3(162.1)	361.4(113.5)	0.208	0.649
	Median	341.6	329		
	Range	102.8 – 841.4	202 -540.2		
2.	*VCAM-1* (II)				
	x (SD)	439.8 (171.6)	556.0 (130.4)	8.040	0.005
	Median	440.2	555.6		
	Range	126 - 897.2	307.4 -970.6		
3.	*VCAM-1* (III)				
	x (SD)	556.4 (243.8)	753.9 (260.8)	12.814	< 0.001
	Median	529.3	696.6		
	Range	206.8 – 1179	449 - 1662.4		

Note:
VCAM-1 levels were in ng/ml
Z_{M-W} = Mann-Whitney Test
I : Observations during the 12 weeks of pregnancy
II : Observations during the 34 weeks of pregnancy
III: Observations during the 2 weeks post delivery
The average value for *VCAM-1* levels in the non-pregnant females were 362.2 (153.7) ng/ml

Table 4. Comparisons of platelets aggregation profiles between treated and untreated groups

No	*Variables*		*Groups*		*P value*
			Treated (n=32)	Untreated (n=34)	
1.	Platelets aggregation (I)				
		Hiper	9 (28.1)	12 (35.3)	0.821
		Hipo	3 (9.4)	3 (8.8)	
		Normo	20 (62.5)	19 (55.9)	
2.	Platelets aggregation (II)				
		Hiper	12 (35.3)	16 (47.1)	0.401
		Hipo	4 (11.8)	4 (11.8)	
		Normo	18 (52.9)	14 (41.2)	
3.	Platelets aggregation (III)				
		Hiper	15 (44.1)	18 (52.9)	0.479
		Hipo	4 (11.8)	5 (14.7)	
		Normo	15 (44.1)	11 (32.4)	

Note:
I : Observations during the 12 weeks of pregnancy
II : Observations during the 34 weeks of pregnancy
III: Observations during the 2 weeks post delivery
P value were calculated based on chi square test

Table 3 shows that although there were no significant differences during the 12 weeks of pregnancy between the treated and untreated groups, there was a significant difference in the increased VCAM-1 levels during the 34 weeks pregnancy between the two groups ($p = 0.005$). The difference was even greater during the 2 weeks post delivery ($p < 0.001$).

During the 1st 12 weeks of pregnancy, VCAM-1 levels were comparable to the non-pregnant individuals and have not yet increased. VCAM-1 levels were gradually increased with the progression of the pregnancy (as detected at 34 weeks) as the uterus started to cause pressure of the pelvic veins. Subsequently, the pressure result in the increasing distention of pelvic and lower limbs veins, causing endothelial injury marked by the increasing levels of VCAM-1.[9-11] A venographic study of pregnant women during the last 3rd semester has shown a narrowing of the Inferior vena cava[12-13]. Moreover, there was a reduced velocity of blood flow in the femoral veins in accordance with the enlargement of the uterus particularly during the last trimester of pregnancy[14]. The increased levels of progesterone and estrogen during the pregnancy also contributed in the vein dilatation, as progesterone has been known to have an effect in decreasing smooth muscle tension including vein's endothelial walls thus causing further veins dilatations even up to 150% throughout the pregnancy[15-18]. The veins dilatation only started to return normally within 8-12 weeks post delivery[18-19].

VCAM-1 levels found in the treated group were not as elevated as in the untreated group. These data suggested that excessive endothelial injury and distention of the veins were able to be prevented by the usage of elastic stockings[10-12]. Moreover, a significant difference in the VCAM-1 levels during the 2 weeks post delivery revealed not only that the usage of elastic stockings prevent further distention of the veins, but also contribute in the more rapid healing process of the endothelial injury[13-18].

The increasing levels of VCAM-1 during the pregnancy were found to be not as high as in patients with eclampsia. This finding suggest that the endothelial injury in varicoses is restricted compared to the eclampsia where the massive endothelial injury presents systemically[19-20]. Furthermore, in a study performed by Scurr dan Sparey, it was shown that a decrease in the velocity of blood flow within the veins did not cause a massive endothelial injury compared to the endothelial injury within the arteries[21-23].

As shown on Table 4, platelets aggregation profiles were not significantly altered among the groups of treated, untreated, during the 12 weeks, 34 weeks of pregnancy, and 2 weeks post delivery. The slight increase in the platelets aggregation profile due to the presence of the veins endothelial injury was apparently not significant (P value > 0.01).

As shown on Table 5, there were no significant differences in the diameter of left femoral veins between the treated and untreated group during the 12 weeks of pregnancy. However, there were a significant increase in the diameter of left femoral veins during the 34 weeks of pregnancy ($p < 0.001$) as well as during the 2 weeks post delivery ($p < 0.001$) between the treated and untreated groups. The left femoral veins diameter in the untreated group were

significantly less dilated compared to those in the untreated group.

Table 5. Comparisons of Left and Right femoral veins diameters in treated and untreated groups

No.	*Femoral veins*	*Observations*	*Groups*		Z_{M-W}	*P value*
			Treated (n=32)	Untreated (n=34)		
1.	Left	I			0.161	0.872
		x (SD)	0.80 (0.07)	0.81 (0.07)		
		Median	0.79	0.79		
		Range	0.64-0.92	0.64-0.92		
		II			3.477	<0.001
		x (SD)	0.83 (0.07)	1.02 (0.35)		
		Median	0.82	0.89		
		Range	0.69-1.0	0.78-1.95		
		III			5.276	<0.001
		x (SD)	0.90 (0.30)	1.30 (0.68)		
		Median	0.82	1.00		
		Range	0.5-1.91	0.85-3.03		
2.	Right	I			1.757	0.079
		x (SD)	0.79 (0.07)	0.76 (0.07)		
		Median	0.78	0.76		
		Range	0.64-0.92	0.60-0.92		
		II			3.163	0.002
		x (SD)	0.84 (0.09)	0.88 (0.05)		
		Median	0.82	0.89		
		Range	0.72-1.23	0.78-0.99		
		III			5.060	<0.001
		x (SD)	0.88 (0.26)	0.99 (0.11)		
		Median	0.82	0.98		
		Range	0.69-1.71	0.85-1.52		

Note:
Measurements of vein diameters were in centimeters
Z_{M-W} = Mann-Whitney Test
I : Observations during the 12 weeks of pregnancy
II : Observations during the 34 weeks of pregnancy
III: Observations during the 2 weeks post delivery
The average diameter of Femoral veins in the non-pregnant females were (left) 0.81(0.07) cm and (right) 0.81(0.07) cm

Starting from the beginning of the 12 weeks of pregnancy plasma volume is slightly increased, whereas from the 24 weeks onwards it is increasing enormously until its peak at around 34 weeks[18]. The increasing pressure caused by the enlarged uterus causes a raise in the internal pressure within the pelvic veins which subsequently was followed by the increased pressure within the lower limbs veins resulting in distention of the veins. Without any adequate treatments this process will result in varicoses[21-24].

Conclusions

Generalized Conclusions

1. The untreated group of primigravida which was not wearing elastic stockings had significantly larger veins diameter

compared to the treated group wearing elastic stockings
2. The incidence of reflux blood flow was only found in the untreated group.
3. The increased levels of VCAM-1 in the untreated primigravida were significantly higher than the treated group.
4. There was no significantly difference in platelets aggregation profiles between treated and untreated groups.

Specified Conclusions

1. The progression of varicoses is marked by increased levels of VCAM-1 as a result of endothelial injury in the distended veins and valve dysfunction.
2. There is a strong correlation between the veins dilatation and the levels of endothelial injuries, shown by the increase of VCAM-1 in accordance with the increasing veins dilatation.
3. Primigravida with level of VCAM-1 higher than 478 ng/ml have a 2.67 increase risk in developing varicoses (with 71.2% confidence) compared to those with lower levels of VCAM-1.
4. Primigravida with level of VCAM-1 higher than 478 ng/ml without elastic stockings will have an increased risk to develop varicoses as high as 41.9% compared to those wearing elastic stockings.
5. In this study, it was found that reflux in the *sapheno-femoral junction* occurred in 6 cases (17.6%) of the untreated group and among them 2 cases (5.9%) were permanently present until 2 weeks post delivery.
6. Mild varicoses never occurred in the treated group, on the other hand 3 cases of mild varicoses were found in the untreated group and found to persist until 2 weeks post delivery.
7. There was a significant difference in the dilatations of femoral veins between the cases with reflux and without reflux ($p < 0.032$).

Theoretically, there are many predisposing factor in the development of varicoses in females. However this study has shown that most importantly, the initiation of varicoses was started by the presence of veins dilatations which then caused endothelial injury marked by increased levels of VCAM-1. The usage of elastic stockings has shown to significantly reduce the dilatation of lower limbs and pelvic veins, thus reducing excessive endothelial injury marked by lower levels VCAM-1. This treatment is shown to effectively prevent the risk of varicoses developments in pregnancy. Another essential finding shown in this study was that platelets aggregation profiles were not significantly altered following the endothelial injury in the development of varicoses[21-24].

Suggestions and Recommendations

Several suggestions proposed based on this study are as follow:

1. Academically
   1.1. Further studies are required to distinguish the main cause of lower limbs and pelvic veins dilatation as the initial process in the development of varicoses in pregnancy.
   1.2. Further studies are also required to determine other vaso-active components present in veins endothelial injury.

1.3. Further studies are required to elucidate the incidence of varicoses in subsequent pregnancy up to menopause in a population of studied primigravida wearing elastic stockings.

2. Practically
   2.1. It is suggested that all pregnant women should wear elastic stockings starting from their 1st pregnancy no later than 12 weeks of pregnancy to reduce the risk of varicoses development.
   2.2. Individuals with risks to develop varicoses during pregnancy are recommended to wear elastic stockings as early as 12 weeks of pregnancy.
   2.3. The Colour Duplex Ultrasound examination is particularly useful to distinguish the varicoses progression from other causes in primigravida with VCAM-1 levels higher than 478 ng/ml.

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