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## Effect of Progesterone and Pregnancy on the Development of Varicose Veins

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**SUMMARY** The aim of this study was to investigate the contribution of progesterone in the development of primary varicose veins on lower limbs during pregnancy. In 50 primiparae with varicose veins, serum progesterone level was quantitatively determined in the 14<sup>th</sup> week of pregnancy and results were compared with those obtained in a control group of 25 primiparae without visible varicose veins. The mean serum progesterone concentration recorded in pregnant women with dilated veins ( $159.9 \pm 15.8$  nmol/L) was significantly higher as compared with the control group ( $159.9 \pm 15.8$  nmol/L vs.  $40.4 \pm 1.6$  nmol/L;  $P < 0.0001$ ). These findings supported the role of hormonal factor in the development of varicose veins in women.

**KEY WORDS:** varicose veins, pregnant women, progesterone

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### INTRODUCTION

Alterations in the lower limb venous circulation are among the most common diseases affecting humans in western world today (1-4), and can impair the patient quality of life. The incidence of varicose veins increases with age and, in addition, is more prevalent and begins earlier in females (1,4), although a recent population-based study found a male predominance (5). Data on varicose veins can already be found in the Ebers papyrus and Corpus Hippocraticus (6). In 1555, Marianus Sanctus believed the cause of varicose veins to be

pregnancy, labor and long standing. At that time, some authors thought that dilated veins in female developed as a consequence of stopping menses during pregnancy, with accumulation of blood in the legs (7).

Current views on the pathogenesis of varicose veins include a number of factors, the most important being genetic, mechanical, hemodynamic and hormonal factors. In females, the disease manifests frequently during pregnancy, so many investigators have assigned a major role to the

hormonal factors such as estrogens and progesterone (8,9).

In this study, we investigated the level of progesterone during pregnancy in women with and without varicose veins in order to detect the possible correlation between the level of progesterone and the development of primary varicose veins.

### SUBJECTS AND METHODS

During a two-year period (2003-2005), we studied 75 pregnant women at University Department of Dermatology and Venereology, Rijeka University Hospital Center. Patients were enrolled after signing an informed consent and were divided into two groups: group 1 included 50 pregnant patients with varicose veins, and group 2 (control group) included 25 pregnant women without varices. Patients were included if they were primigravidae, if they were not standing at work, and if they had never used hormonal contraceptives. Patients with renal diseases, hypertension, other diseases or undertaking hormonal therapy were excluded. Their age and weight were also recorded. Serum level of progesterone was determined in all patients in the 14<sup>th</sup> week of pregnancy. After median cubital vein venepuncture, blood samples were collected in test tubes and determination was made with the Coat A Count Progesterone technique, a solid phase radioimmunoassay for quantitative measurement of progesterone (10) at Department of Nuclear Medicine, Rijeka University Hospital Center. Statistical analysis was done by use of Mann-Whitney test (using GraphPad InStat version 3.05 for Windows, GraphPad Software, San Diego, CA, USA, www.graphpad.com). Two-tailed *P* values of less than 0.05 were considered statistically significant.

### RESULTS

The median age of study women was 24 years in both groups (range 20-28 in group 1 and 21-29 in group 2). The two groups were not significantly different according to any baseline clinical and demographic characteristic analyzed (*P*>0.05) (Table 1). Out of 50 patients with varicose veins (group 1), 13 (26.0%) had symptoms that included heaviness, tired legs, itching and aching sensations (CEAP class 1-2). The two groups differed significantly according to the mean blood concentration of progesterone (*P*<0.0001) (Fig. 1). In the group of pregnant women with varicose veins, the mean progesterone concentration was 159.9±15.8 nmol/L (ranging from 112.0 to 172.1 nmol/L), where-

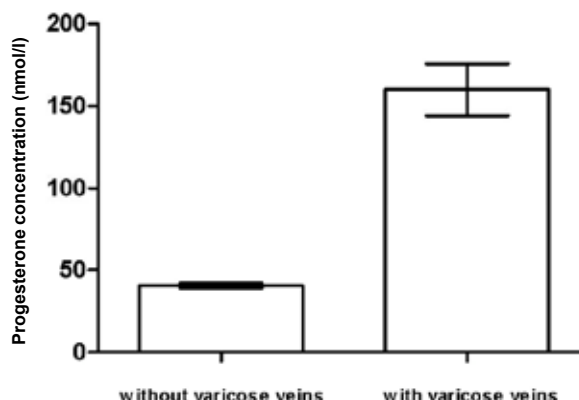
**Table 1.** Demographic characteristics of the pregnant women included in the study.

	Primiparae with varicose veins	Primiparae without varicose veins
No. of cases	50	25
Age (yrs)	26 (20-28)	24 (21-29)
Mean weight (kg)	68	66
Week of pregnancy	14 <sup>th</sup>	14 <sup>th</sup>
Primigravida	All	All

as in the control group (group 2) it was 40.41±1.6 nmol/L (ranging from 37.9 to 42.3 nmol/L) (Fig. 1). In pregnant women with varicose veins, the mean progesterone level was fourfold that recorded in control group.

### DISCUSSION

Varicose veins are dilated, tortuous or serpentine veins, which develop on lower limbs. The pathogenesis has not yet been fully clarified. In lower limbs, the venous blood flow is normally directed upwards and inwards. Incompetent valves, thrombosis or elevated venous pressure cause changes in the venous circulation and later in the skin, i.e. lead to the chronic venous disease. The theory that primary varicose veins lead to valvular incompetence receives ever more attention (11). Although animal models can contribute in clearing some aspects of varicose veins (12), the accessibility of skin veins makes them an excellent object to examine the effects of hormones on veins in pregnancy. Progesterone and estrogen have numerous effects on the vascular system (8,9,13). Recent epidemiological studies have found that varicose veins of the superficial venous system of lower extremities develop more frequently in



**Figure 1.** Progesterone concentration in pregnant women in the 14<sup>th</sup> week of pregnancy (expressed as mean and standard deviation).

women and occur more frequently during pregnancy (1-4), with the highest prevalence in multiparous women (14). However, the prevalence of varicose veins is lower among women in developing countries, although on an average they have more pregnancies than women in industrialized countries (15).

The study results pointed to a significant difference in plasma progesterone concentration between women with and without varicose veins in the 14<sup>th</sup> week of pregnancy. Varicose veins were more commonly found in pregnant women with higher serum progesterone concentration. Although the level of progesterone varies individually among non-pregnant women, it normally ranges between less than 1 nmol/L and 20 nmol/L. This range depends on the phase of the menstrual cycle, being higher during the luteal phase when progesterone increases. During pregnancy, the level of progesterone steadily increases. Progesterone can act through binding to progesterone receptors expressed in the nuclei of cells of the venous walls, leading to hypotonia of their smooth muscles and inhibiting the synthesis of collagen fibrils, with consequential vasodilatation and perhaps valvular reflux (16,17). This is not the only factor that can play a role in the development and manifestation of varicose veins during pregnancy. The mechanical factor, i.e. compression of iliac veins, probably by enlarging the gravid uterus, is also important, especially in later pregnancy (18). An additional mechanism that may contribute to the formation of primary varicose veins is the increase in the plasma volume in pregnant women. Estrogens and progesterone increase the plasma volume by decreasing protein diffusion through capillary endothelium. The expected rise in blood pressure does not occur because of vasodilatation (19).

Our findings are consistent with previous studies that also found a correlation between the level of progesterone and the development of varicose veins (16,20,21).

## CONCLUSION

Although the number of study women was relatively small, our preliminary results supported the hypothesis on the increase in the level of blood progesterone to be important for the development of primary varicose veins in early pregnancy. Clinically, progesterone determination in pregnant women may prove useful for the early prevention of varicose veins by wearing compression stockings.

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