Karya J Health Sci. 2022; 3(2): 150-153
ARAŞTIRMA MAKALESİ/RESEARCH ARTICLE doi: 10.52831/kjhs.1047838 e-ISSN:2717-9540

KARYA JOURNAL OF HEALTH SCIENCE

journal homepage: www.dergipark.org.tr/kjhs

THE ETIOLOGICAL FACTORS OF THE LOWER EXTREMITY VENOUS INSUFFICIENCY IN PREGNANCY

GEBELİKTE ALT EKSTREMİTE VENÖZ YETMEZLİĞİNİN ETYOLOJİK FAKTÖRLERİ

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ABSTRACT

Objective: Number of pregnancy has a positive correlation with the development of lower limb venous insufficiency. We purpose to reveal the relation between the venous insufficiency in pregnancy and concomittant gestational features.

Method: A retrospective analysis was performed using data collected from the database of our institution between January 2016-January 2021. 35 patients were included. The informations about age, in vitro fertilisation usage, polycystic ovary syndrome (PCOS), free T4 (fT4) and TSH levels, gestational diabetes mellitus (DM), other features and reports of Doppler ultrasound (USG) were investigated. Quantitative variables were analysed using Kolmogorov-Smirnov test. The relation between qualitative variables were analysed using x^2 test. Descriptive statistics of qualitative variables were considered as mean±standard deviation, median (25-75 percentile), minimum-maximum. Descriptive statistics of quantitative variables were considered as frequency (%). P <0.05 was considered as statistically significant.

Results: At the time of complain about leg pain and edema in lower extremities, 60% of patients were primigravid, mean age was 28.91±6.94. Mean value of the week of pregnancy was 28.71±7.92 (12-38). Mean value of TSH and fT4 were 1.74±0.86 mIU (0.23–4.07) and 13.78±3.15 pmol/mL (5.06-7.61) respectively. Twelve patients (34.3%) had venous insufficiency in Doppler USG, 3 (25%) of them were in 2nd trimester, 9(75%) were in 3rd trimester. 41.6% had normal delivery and 58.3% had cesarian section previously. fT4/TSH ratio was 9.98 in Doppler USG positive group and in 3rd trimester had TSH and fT4 level as 1.55±0.44 and 14.62±2.14 respectively.

Conclusion: There wasn't a close relation between symptoms and venous insufficiency in Doppler USG neither between venous insufficiency and number of pregnancy or previous method of delivery. Even though venous insufficiency increases in the 3rd trimester, venous insufficiency didn't correlate with TSH and fT4 levels. The ratio of fT4/TSH was sligtly higher in patients with venous insufficiency.

Key Words: Venous Insufficiency, Pregnancy, Thyroid Hormone

ÖZ

Amaç: Gebelik sayısı, alt ekstremite venöz yetmezlikle pozitif korelasyon gösterir. Çalışmamızda gebelikteki venöz yetmezliğin, gebeliğe eşlik eden özellikler ile korelasyonunu incelemeyi amaçladık.

Yöntem: Ocak 2016- Ocak 2021 arasında hastanemize başvuran 35 hasta retrospektif olarak incelendi. Yaş, in vitro fertilizasyon, PCOS, sT4 ve TSH düzeyleri, gestasyonel DM ve diğer özellikler ile Doppler USG raporları incelendi. Nicel değişkenler Kolmogorov-Smirnov testiyle incelendi. Nitel değişkenler x^2 test ile incelendi. Tanımlayıcı istatistikler, ortalama±standard sapma, median (25-75 yüzdelik), minimum-maksimum olarak değerlendirildi. Nicel değişkenlerin tanımlayıcı istatistiği ise frekans (%) olarak değerlendirildi. P<0.05 istatistiksel anlamlı kabul edildi.

Bulgular: Bacak ağrısı ve ödemi gelişmesi anında, %60 hasta primigraviddi. Ortalama yaş 28.91±6.94 idi. Ortalama gebelik haftası 28.71±7.92 (12-38) idi. Ortalama TSH ve sT4 değeri, 1.74±0.86 mIU (0.23–4.07) ve 13.78±3.15 pmol/mL (5.06-7.61) idi. On iki hastada (%34) Doppler USG'de venöz yetmezlik mevcuttu. Bu hastaların 3'ü (%25) 2. trimester, 9'u (%75) 3. trimesterdeydi. % 41.6'sı normal doğum ve %58.3'ü Cesarian ile daha önce doğum yapmıştı. ST4/TSH oranı, Doppler pozitif grupta 9.98 idi. 3. trimesterde TSH ve sT4 düzeyleri sırasıyla 1.55±0.44 ve 14.62±2.14 idi.

Sonuç: Semptom varlığı ve Doppler USG'de venöz yetmezlik oluşu arasında yakın bir ilişki tespit edilemedi. Aynı şekilde venöz yetmezlik ile gebelik sayısı ve önceki doğum metodu arasında yakın ilişki bulunamadı. Venöz yetmezlik 3. trimesterde artsa da, venöz yetmezlik TSH ve sT4 düzeyleri ile korelasyon göstermiyordu. ST4/TSH oranı venöz yetmezlik gösteren gebelerde ılımlı artmıştı.

Anahtar Kelimeler: Venöz Yetmezlik, Gebelik, Tiroid Hormonu

Makale Bilgisi/Article Info

Yükleme tarihi/Submitted: 27.12.2021, **Revizyon isteği/Revision requested:** 23.01.2022, **Son düzenleme tarihi/Last revision received:** 09.08.2022, **Kabul/Accepted:** 16.08.2022

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INTRODUCTION

The prevalence of the lower extremity venous insufficiency is approximately 60–65% in the adult population [1]. Etiological factors include lack of physical activity or sedentary lifestyle, and obesity [1]. Furthermore genetic tendency, female gender, female sex- hormones pregnancy and multi-parity can also be the reasons of venous insufficiency [1]. Hypertension, older age, smoking, constipation, low intake of fibrous food may lead venous insufficiency [2]. May-Thurner syndrome, Klippel–Trenaunay syndrome, polymorphism of collagen-encoding genes are likely additional causes of this disease [1].

According to several studies, number of pregnancies have a positive correlation with the development of lower limb venous insufficiency, however the physiological mechanism remains unclear [3–5]. Possible factors are the mechanical obstruction of the veins in the pelvic cavity, hormonal effects that cause smooth muscle dilatation, and the increase of physiolocigal blood volume needing in pregnancy [6,7]. In a normal progress of pregnancy, the incidence of lower extremity venous insufficiency is found to be 17% [5]. Gardenghi and collegues evaluated pregnant women during pregnancy using Doppler ultrasound to investigate the degree of venous insufficiency. Gardenghi revealed that there is no relation between lower extremity edema and venous insufficiency. In addition, he found the edema in legs decreased spontaneously in postpartum period [5,8].

Thyroid hormone level changes may occur during pregnancy and have many effects on both mother and baby [9]. In addition it's been reported that hypertyroidism is responsible of restless leg in pregnancy [10]. However there is no study that investigates the incidence of edema and restless leg syndrome in pregnancy and its relation with concomittant pregestational and gestational features. We purpose to reveal the relation between the venous insufficiency in pregnancy and concomittant gestational features.

METHOD

A retrospective analysis was performed using data collected from the database of our institution between January 2016-January 2021. The data corresponding to consecutive patients subjected to routine diagnostic procedures of pregnant patients who declareted leg pain and edema in lower extremities. In the first step we collected information about age, number of pregnancy, number of delivery, number of twin pregnancy, in vitro fertilisation usage, polycystic ovary syndrome (PCOS), fT4 and TSH levels, gestational diabetes mellitus (DM), previous method of delivery of each. In addition, the week of gestation in which the leg pain complain occured was determined. Also the reports of patients' Doppler ultrasound examinations were collected. 35 patients were included in the study.

The patients were examined by an ultrasound of their lower extremity venous system using Toshiba Aplio 500 (TOSHIBA/Canon Medical Systems Co., Otawara, Tochigi, Japan) with a linear probe (3–11 MHz) by different radiologists.

TSH and fT4 concentrations were determined by electrochemiluminescence immunoassay (ECLIA) methods on COBAS 8000 (c702) biochemical analyser (Roche Diagnostics GmbH; Mannheim, Germany). Reference ranges were in 0.27-4.2 μIU for TSH and 12-22 pmol/mL for fT4.

Statictical Analysis

Finally, collected data was analyzed using SPSS 22.0 (SPSS Inc., Chicago, IL). Quantitative variables were analysed using Kolmogorov-Smirnov test suitable for normal distribution. Independent samples were compared with t-test for normal distribution and with Mann-Whitney U test for abnormal distribution. The relation between qualitative variables was analysed using x^2 test. Descriptive statistics of qualitative variables were considered as mean±standard deviation, median (25-75 percentile), minimum-maximum.

Descriptive statistics of quantitative variables were considered as frequency (%). P <0.05 was considered as statistically significant.

Ethical Approval

Ethical approval for this study was obtained from the institutional review board (14/04/2021-8/V).

RESULTS

In our study the inclusion criteria were pregnancy, leg pain and edema in lower extremities, the exclusion criteria were deep venous thrombosis, peripheral arterial disease, lymphedema. 35 patients who had leg pain and edema, were included in the study.

Mean age was 28.91±6.94, mean value of the week of pregnancy in which leg pain occured was 28.71±7.92 (12-38). Mean value of TSH was 1.74±0.86 μIU (0.23–4.07) and in normal range, and mean value of fT4 was 13.78±3.15 pmol/mL (5.06–17.61) and in normal range. The median number of previous pregnancy was 1 and number of previous delivery was zero at the time of complains (Table 1).

Table 1. Descriptive statistics of quantitative variables

Patients (n=35)	**x̄±SD**	**Min-Max**
Age	28.91±6.94	18–42
Week of pregnancy	28.71±7.92	12–38
TSH (μIU)	1.74±0.86	0.23–4.07
fT4 (pmol/mL)	13.78±3.15	5.06–17.61
Patients (n=35)	**Median (IQR)**	**Min-Max**
fT4/TSH	7.69 (5.51-12.67)	2.39–72.17
Previous number of pregnancy	1 (1-2)	1-5
Previous number of delivery	0 (0-1)	0–3

x̄±SD:Mean±standard deviation, IQR: Interquartile range(25%–75%)

At the time of complaint about leg pain and edema in lower extremities, 21 (60%) patients were primigravid (Table 2).

Table 2. Descriptive statistics of qualitative variables of 35 patients.

Variables	**n (%)**
Twin pregnancy	1 (2.9)
IVF pregnancy	2 (5.7)
1 (primigravid)	21 (60)
>1 (multigravid)	14 (40)
Polycystic ovary syndrome (PCOS)	None
Gestational DM	1 (2.9)
Previous method of delivery	
Normal	14 (40)
Cesarian sectio	20 (57.1)
None (recurrent miscarriage)	1 (2.9)
Venous insufficiency in Doppler USG	12 (34.3)
Grade in Doppler USG	
None	23 (65.7)
Bilateral grade 1	1 (2.9)
Bilateral grade 2	1 (2.9)
Bilateral grade 4	3 (8.6)
Left grade 3	3 (8.6)
Left grade 4	3 (8.6)
Right grade 2	1 (2.9)

Patients who had venous insufficiency in Doppler USG or not, had been evaluated in regards of age, week of pregnancy in which leg pain occured, number of pregnancy, number of previous delivery, difference of TSH, fT4, fT4/TSH ratio (Table 3).

Table 3. Descriptive statistics of quantitative variables and results

Variables	Venous insufficiency in Doppler USG		p
	Absent (n=23)	Present (n=12)	
Age	28.52±7.46	29.67±6.05	0.650
The week of pregnancy in which leg pain occured	27.30±7.83	31.42±7.70	0.148
TSH (µIU)	1.84±0.97	1.56±0.61	0.358
fT4 (pmol/mL)	13.54±3.46	14.23±2.51	0.545
fT4/TSH	7.22 (5.06-12.67)	9.98 (6.60-12.87)	0.151
Gestastional DM			
Present	1 (4.3)	0 (0)	1.000
Absent	22 (95.7)	12 (100)	
Previous method of delivery			
Absent	1 (4.3)	0 (0)	
Normal	9 (39.1)	5 (41.7)	1.000
Cesarian sectio	13 (56.5)	7 (58.3)	

Mean age, week of pregnancy in which leg pain occured, fT4, fT4/TSH ratio were higher for patients who had venous insufficency in Doppler USG. However the difference between two groups, was not statistically significant (p>0.05) (Table 3).

On the contrary patients who didn't have venous insufficiency in Doppler USG evaluations, the number of previous pregnancy and previous delivery were higher. Solely the difference was not statistically significant (p>0.05). In addition, positive Doppler USG signs do not have a statistically significant relation with twin pregnancy, IVF pregnancy, gestational DM, previous method of delivery, and previous number of pregnancy (p>0.05) (Table 2).

When we investigated 12 patients who had positive findings of venous insufficiency in Doppler USG, 3 (25%) patients were in 2nd trimester, 9 (75%) were in 3rd trimester (p=1.000). 5 (41.6%) patients received normal delivery, 7 (58%) Cesarian section (Table 3). 1 patient had IVF pregnancy as well as 1 patient had twin pregnancy (0.08% and 0.08%, p=1.000). In addition 8 (66.6%) patients were primigravid at the time of investigation and 4 (33.3%) were multigravid (p=1.000) (Table 2). The mean TSH level in patients with or without positive Doppler finding were 1.56±0.6 µIU and 1.84±0.9 µIU respectively, however it wasn't statistically significant (p=0.358). Similarly the fT4 level in patients with or without positive Doppler finding were 14.23±2.51 pmol/mL and 13.78±3.15 pmol/mL respectively, and it was not statistically significant either (p=0.545). Also we found higher mean value of fT4/TSH ratio as 9.98 (6.60-12.87) for patients who had positive Doppler USG findings (p=0.151). Moreover in 3rd trimester in which higher ratio of venous insufficiency was present, TSH and fT4 concentrations were 1.55±0.44 and 14.62±2.14. In addition these levels were 2.03±0.85 and 12.95±3.61 respectively in group without venous insufficiency (Table 3).

DISCUSSION

The lower limb edema may be present in the second and the third trimesters of pregnancy and it can be resolved in postpartum period spontaneously [8]. As Gardenghi and collegues determine that the edema is not associated with venous reflux [8], we preferred to choose leg pain and edema together as the main complains, and we aimed to determine the relation between 'leg pain and edema of lower extremities and the finding of Doppler USG' in pregnancy. Moreover we purpose to find out underlying etiological factors.

Lower limb venous return may be affected by changes caused by pregnancy with respect to the enlarged uterus compressing the inferior vena cava and iliac veins [5]. The venous muscle pump has a tendency to decrease in the 3rd trimester mostly [5]. Regardless of competent venous valves, pregnancy hormones as estriol, estradiol and progesterone, may affect the venous distensibility and competent venous valves become temporarily incompetent [5]. Struckmann explains that three months post partum, symptoms including fullness, cramps, unrest, itch, swollen legs, pain disappeare. In our study, patients having leg pain and edema were included and evaluated with Doppler USG, and symptoms were matched with Doppler evaluation. The ratio of venous insufficiency in pregnancy is found to be 5-10% [5]. In our study 12 (34.2 %) patients had Doppler USG findings about venous insufficiency (p=1.000). Therefore we believe that there is not a close relation between symptoms and venous insufficiency in pregnancy, either.

The incidence of developing varicose veins correlates with the number of pregnancies as proposed in İsmail and colleagues' study [11]. In addition, Szary et al. concluded that one of the most important factors for the development of venous disease is pregnancy, moreover multiparity [1]. They also found that the risk of venous insufficiency was 20% in nulliparous, 41% in primiparous women, and increased with each next pregnancy [1]. The probable reason is the overload of the venous system caused by the compression by enlarged uterus in late pregnancy [1]. However, Edinburgh Vein Study doesn't correlate with the relation between varicose veins and pregnancy, so there is a conflict in literature about the issue [12]. In our study, 12 patients (34.2%) who had Doppler USG findings, were classified into two groups in regard of number of gravida: 8 (66.6%) patients were primigravid, 4 (33.3%) patients were multigravid (p=1.000). We concluded that development of venous insufficiency has no relation with the number of pregnancy. However the number of patients can be found inadequate.

Based on the week of pregnancy in 12 patients who had leg pain, edema and Doppler USG findings, we obtained that, 3 (25%) patients were in 2nd trimester, and 9 (75%) were in 3rd trimester (p=1.000). Even though it is not statistically significant, the increased ratio of venous insufficiency in last trimester is similar to the literature [5].

In regards of previous delivery methods, 5 (41.5%) patients of the 12 patients who had leg pain, edema and Doppler USG findings, had normal delivery, and 7 (58.3%) had Cesarian section (p=1.000). Unfortunately, we could not find any statistical significance between venous insufficiancy and previous methods of delivery.

Thyroid hormones changing during pregnancy are related with increased risk of miscarriage, preterm delivery, placental abruption, low birth weight and fetal loss, hypertension [9]. During pregnancy, hypothyroidism is not rare. It has been reported that 3-15% of pregnant women suffer from subclinical hypothyroidism [10]. We found the mean TSH levels in patients with or without positive Doppler finding were 1.56±0.6 µIU and 1.84±0.9 µIU respectively, however it wasn't statistically significant (p=0.358). Similarly the fT4 levels in patients with or without positive Doppler finding were 14.23±2.51 pmol/mL and 13.78±3.15 pmol/mL respectively, and it was not statistically significant either (p=0.545). Also we found higher mean values of fT4/TSH ratio as 9.98 (6.60-12.87) for patients who had positive Doppler USG findings (p=0.151).

Pereira proposed that pregnancy associated with hyperthyroidism can induce restless leg symptoms, however it's not related to venous insufficiency [13]. As far as we know, there is no study in literature that determines the relation between the thyroid levels and venous insufficiency in pregnancy and in our study, venous insufficiency did not correlate with TSH and fT4 levels. However the ratio of fT4/TSH levels was sligtly higher in pregnant patients who had venous

insufficiency. It's needed to be investigated further to determine whether the correlation is present.

When we investigated the relation between TSH, fT4 levels and venous insufficiency in patients suffering from venous insufficiency in 3rd trimester, we didn't find any correlation.

Study Limitations

Due to the small size of study group, the relation between gestational DM, previous method of delivery, PCOS, twin pregnancy and IVF pregnancy with venous insufficiency couldn't be determined thoroughly.

CONCLUSION

We concluded that;

1. There is not a close relation between symptoms and venous insufficiency in pregnancy.

2. The development of venous insufficiency has no relation with the previous number of pregnancy.

3. There is no relation between venous insufficiency and previous method of delivery.

4. In the 3rd trimester, venous insufficiency increases.

5. Venous insufficiency does not correlate with TSH and fT4 levels. However the ratio of fT4/TSH levels is sligtly higher in pregnant patients who have venous insufficiency.

6. We didn't find any correlation between TSH, fT4 levels and venous insufficiency in patients suffering from venous insufficiency in the 3rd trimester.

7. The relation between gestational DM, previous method of delivery, PCOS, twin pregnancy and IVF pregnancy with venous insufficiency couldn't be determined due to the inadequate number of patients.

Small number of patients in our study may be found inadequate, however further clinical studies should be conducted to reach more significant results particularly different etiological factors of venous insufficiency in pregnancy.

Ethical Approval: *2021/8-V, Muğla Sıtkı Koçman University Institutional Ethical Review Board*
Conflict of Interest: *The authors have no conflicts of interest to declare.*

Funding: *None.*

Acknowledgements: *None.*

Author Contribution: Concept: *Hİ,BHK,NÇ,Gİ;* ***Desing:*** *Hİ,BCD,Gİ;* ***Data collecting:*** *SY,BCD,FTS,KA,BH;* ***Statistical analysis:*** *Hİ,SY,BCD,KA;* ***Literature review:*** *FTS,KA,SY,BH;* ***Writing:*** *Hİ,BHK,NÇ;* ***Critical review:*** *BH,Gİ,BHK,FTS,NÇ.*

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