



Clinical Importance of the First Trimester Uterine Artery Doppler Measurements in Patients with Hyperemesis Gravidarum

Birinci Trimester Uterin Arter Doppler Ölçümlerinin Hiperemesis Gravidarumlu Hastalarda Klinik Önemi

Mustafa MARAŞLI¹, Esra KELEŞ², Pınar YILDIZ³, Mehmet Mete KIRLANGIÇ¹, Rezzan Berna BAKI¹, Emre MAT², Gazi YILDIZ¹, İlknur ADANIR⁴, Banu DANE⁵

¹University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye

²University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Gynecologic Oncology, İstanbul, Türkiye

³Ümraniye Training and Research Hospital, Clinic of Perinatology, İstanbul, Türkiye

⁴Çatalca İlyas Çokay State Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye

⁵University of Health Sciences Türkiye, Başakşehir Çam and Sakura Training and Research Hospital, Clinic of Perinatology, İstanbul, Türkiye

ABSTRACT

Objective: To examine the relationship between the first trimester uterine artery doppler measurements, biochemical markers, first trimester antenatal screening test and severity of hyperemesis gravidarum (HG) according to Pregnancy-Unique Quantification of Emesis (PUQE) score.

Methods: A prospective observational study was carried out in a tertiary university hospital, between December 2016 and March 2017. A total of 207 consecutive singleton pregnancies at 11-13.6 weeks of gestations were enrolled. Sociodemographic, clinical characteristics, PUQE scores, biochemical blood, and urine sample results were collected. First trimester antenatal screening test and uterine artery doppler measurements were performed. The severity of HG was made based on the score of PUQE test.

Results: A total 207 pregnant women enrolled in this study. Of the patients, 131 were in group I and 76 in group II. No significant difference was observed in of first trimester screening serum markers, doppler ultrasonography findings and PUQE scores between the two groups ($p>0.05$). There was no statistically significant difference between the patients in group I and group II in terms of the presence of urinary tract infections. Ketonuria

ÖZ

Amaç: Birinci trimester uterin arter doppler ölçümleri, birinci trimester antenatal tarama testinin biyokimyasal belirteçleri ve Gebeliğe Özgü Bulantı Kusma Şiddetinin Belirlenmesi Ölçeği (PUQE) skoruna göre hiperemesis gravidarum (HG) şiddeti arasındaki ilişkiyi incelemektir.

Yöntemler: Bu prospektif gözlemsel çalışma Aralık 2016 ile Mart 2017 tarihleri arasında üçüncü basamak bir üniversite hastanesinde gerçekleştirildi. 11-13,6 gebelik haftalarında toplam 207 ardışık tekil gebelik çalışmaya kabul edildi. Sosyodemografik, klinik özellikler, obstetrik ve tıbbi öyküler ve antropometrik ölçümler kaydedildi. Daha sonra PUQE skorları, biyokimyasal kan ve idrar örneği sonuçları toplandı. Tüm hastalara birinci trimester antenatal tarama testi ve uterin arter doppler ölçümleri yapıldı. HG'nin şiddeti PUQE testi skoruna göre belirlendi. PUQE test puanına göre hastalar iki gruba ayrıldı. Kontrol grubu (grup I) PUQE puanı <6 olanlar ve çalışma grubu (grup II) PUQE puanı ≥ 7 olanlar idi.

Bulgular: Bu çalışmaya toplam 207 gebe katıldı. Hastaların 131'i grup I'de, 76'sı grup II'de yer aldı. İki grup arasında birinci trimester tarama serum belirteçleri, doppler ultrasonografi bulguları ve PUQE skorları açısından anlamlı fark izlenmedi ($p>0,05$). Grup

Address for Correspondence: Esra Keleş, University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Gynecologic Oncology, İstanbul, Türkiye
E-mail: dresrakeles@hotmail.com **ORCID ID:** orcid.org/0000-0001-8099-8883

Cite this article as: Maraşlı M, Keleş E, Yıldız P, Kırlangıç MM, Baki RB, Mat E, Yıldız G, Adanır İ, Dane B. Clinical Importance of the First Trimester Uterine Artery Doppler Measurements in Patients with Hyperemesis Gravidarum. Bezmialem Science 2024;12(2):212-6



©Copyright 2024 by Bezmialem Vakıf University published by Galenos Publishing House.
Licensed by Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND 4.0)

Received: 22.07.2023

Accepted: 23.01.2024

ABSTRACT

was detected in three patients (2.4%) in group I and 11 patients (17.2%) in group II ($p < 0.01$).

Conclusion: The result of the study showed no significant relationship between the first-trimester uterine artery doppler parameters, biochemical markers and the severity of HG, which was measured according to PUQE scoring system. However, we did find that PUQE test was an effective test in the detection of patients with ketonuria.

Keywords: First trimester, hyperemesis gravidarum, PUQE test, uterine artery doppler

ÖZ

I ve grup II'deki hastalar arasında idrar yolu enfeksiyonu varlığı açısından istatistiksel olarak anlamlı fark yoktu. Grup I'de 3 (%2,4), grup II'de 11 (%17,2) hastada ketonüri saptandı ($p < 0,01$).

Sonuç: Çalışmanın bulguları, birinci trimester uterin arter doppler parametreleri, biyokimyasal belirteçler ile PUQE skorlama sistemine göre ölçülen HG şiddeti arasında anlamlı bir ilişki olmadığını gösterdi. Ancak PUQE testinin ketonüri hastaların saptanmasında etkili bir test olduğu gösterildi.

Anahtar Sözcükler: Birinci trimester, hiperemesis gravidarum, PUQE testi, uterin arter doppler ultrasonografi.

Introduction

Nausea and vomiting of pregnancy (NVP) are extremely common. Up to 90% of women experience nausea during pregnancy. Studies showed that approximately 27 to 30 percent of women experienced only nausea, while vomiting could be seen in 28 to 52% of all pregnancies (1). However, 0.3-3.6% of pregnant patients suffer from the most severe form of NVP known as hyperemesis gravidarum (HG) (2). HG refers to intractable vomiting during pregnancy, leading to weight loss, electrolyte imbalances, dehydration, and volume depletion, resulting in ketonuria (3). There is no consensus on specific diagnostic criteria, but it generally refers to the severe end of the spectrum regarding NVP (4).

The etiology of HG is unknown, but several theories exist. Levels of human chorionic gonadotropin (hCG) levels peak during the first trimester, corresponding to the typical onset of hyperemesis symptoms (5). Estradiol levels increase in early pregnancy and decrease later, mirroring NVP symptoms. Additionally, nausea and vomiting are side effects of estrogen-containing medications (6).

In patients with severe HG, complications including vitamin deficiency, dehydration, and malnutrition may occur if not treated appropriately. Wernicke encephalopathy, caused by vitamin-B1 deficiency, can lead to death and permanent disability if left untreated (7). Additionally, there have been case reports of injuries secondary to forceful and frequent vomiting, including esophageal rupture and pneumothorax (8). Electrolyte abnormalities such as hypokalemia can also cause significant morbidity and mortality (9).

No single measure can easily define, quantify or evaluate the treatment of HG. An English pregnancy-specific questionnaire, Pregnancy-Unique Quantification of Emesis (PUQE), has been developed to assess the severity of emesis in pregnancy. This questionnaire contains three questions regarding the time-span of nausea, vomiting, and retching, respectively, as well as one question assessing the global psychological and physical quality of life.

To our knowledge, there is a large body of research on the relationship between first-trimester uterine artery Doppler

findings and pregnancy complications. However, there is limited research on the use of first-trimester uterine artery Doppler to predict placental abnormalities in cases of HG. Therefore, this study aimed to evaluate the relationship between first-trimester uterine artery Doppler measurements and biochemical markers and PUQE test scores in pregnant women who attended first-trimester prenatal screening.

Methods

This prospective observational study was conducted at the Department of Obstetrics and Gynecology of a Tertiary University Hospital, between December 2016 and March 2017 and comprised singleton pregnant women who attended first trimester prenatal screening. The study was in line with the Helsinki Declaration and approved the Ethics Committee of the Bezmi Alem Vakıf University (decision no: 17/22, date: 07.12.2016). All participants were informed regarding the study and they gave informed consent prior participation.

Inclusion criteria were: singleton pregnancies between 11-13.6 weeks of gestation, absence of any gastrointestinal, audiovestibular, endocrinological, infectious, and psychological disorders that might cause nausea and vomiting, except pregnancy-induced vomiting, and agreed to participate to the study. Exclusion criteria were: multiple pregnancy, molar pregnancy, fetal structural anomaly, and abnormal nuchal fold thickness.

A total of 207 consecutive patients who met the inclusion and exclusion criteria were included in the study. Sociodemographic, clinical characteristics, obstetric and medical histories, and anthropometric measurements were collected. Then, PUQE scores, biochemical blood, and urine sample results were collected. Next, pregnant women underwent first trimester screening and uterine artery doppler ultrasonography using Philips HD11 XE device with 3.5 MHz curvilinear probe. The screening consisted of nuchal translucency (NT) and serum free β -human chorionic gonadotrophin (free β -hCG) and pregnancy-associated plasma protein A (PAPP-A) measurements. Gestational age was determined according to the head-rump distance (CRL) measured in the sagittal plane on abdominal ultrasonography. During the Doppler ultrasonography examination, the probe was placed in the iliac fossa above the level of the inguinal ligament. The uterine artery was

detected where it crossed the external iliac artery by color Doppler imaging. A pulsed Doppler was used to determine the waveform. A resistance-index (RI) and pulsatility-index (PI) were calculated from each uterine artery and the presence or absence of a notch were noted. The same procedure was repeated for the contralateral uterine artery. The urine analysis test was classified according to ketones positivity and urinary tract infection. Those with leukocyte positivity, bacteriuria, or leukocyte esterase positivity were included in the urinary tract infection group.

The 24 h PUQE (10,11) is a self-reported measure of the duration of nausea, episodes of vomiting, and episodes of retching in the last 24 hours on a 5-point scale. A higher score indicates more severe NVP. NVP was evaluated as mild in those with <6 points, moderate in those with 7-12 points, and severe in those with 13 points and above (12). The patients in the mild group were classified as group I, and the patients in the moderate and severe groups were classified as group II.

Statistical Analysis

IBM SPSS 21.0 (Statistical Package for Social Sciences Chicago, USA) was employed to analyze the collected data. When the numerical data fit the normal distribution, analysis between groups was performed using the Student or ANOVA test. The Mann-Whitney test was applied when the data did not conform to the normal distribution. Categorical data were analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

A total 207 pregnant women enrolled in this study. Of the patients, 131 were in group I and 76 in group II.

The mean age of the patients was 29.9±4.9 (range: 18-44 years). The mean age of group I patients was 29.7±5.0 and 30.4±4.8 years in group II. The body mass index (BMI) values of all patients ranged from 15.4 to 34.8, with a mean of 24.6±3.7. The mean BMI of the patients in group I was 24.6±3.7 and in group II was 24.5±3.7 kg/m². No significant difference was found in demographic and obstetric variables between the two groups. The demographic information and obstetric characteristics of the patients are presented in Table 1.

The mean CRL value of patients in group I was 63.3±7.2 and in group II was 61.8±6.5 mm. There was no significant difference between the two groups in CRL measurements (p=0.1). NT measurements varied between 1.1 and 3.0, with a mean of 1.4±0.2 mm. The mean NT value of the patients in group I was 63.3±7.2 and in group II was 61.8±6.5. There was no statistically significant difference between the two groups in terms of CRL measurements (p=0.1). No significant difference was observed in terms of first trimester screening serum markers, and doppler ultrasonography findings between the two groups. There was no statistically significant difference between the patients in group I and group II in terms of the presence of urinary tract infections. Ketonuria was detected in three patients (2.4%) in group I and 11 patients (17.2%) in group II (p<0.01) (Table 2).

No statistically significant difference was observed between sociodemographic, first-trimester uterine artery Doppler measurements and first-trimester screening ultrasonographic and serum markers between mild NVP, moderate NVP, and severe NVP groups (Table 3).

Discussion

The results of the present study indicated that there was no association between the first trimester uterine artery doppler parameters, biochemical markers of the first trimester antenatal screening test and severity of HG according to PUQE score.

Table 1. Baseline demographic and obstetric characteristics

Variables	Grup I (n=131) Mean ± SD	Grup II (n=76) Mean ± SD	p-value
Age	29.7±5.0	30.4±4.8	0.3
Body mass index (kg/m ²)	24.6±3.7	24.5±3.7	0.8
	Grup I n (%)	Grup II n (%)	p-value
Primigravid	53 (40.5)	31 (40.8)	0.9
Multigravid	78 (59.5)	45 (59.2)	
	Grup I n (%)	Grup II n (%)	
Nullipar	64 (48.9)	n=33 (43.4)	
Primipar	42 (32.1)	n=28 (36.8)	0.7
Multipar	25 (19.1)	n=15 (19.7)	

SD: Standard deviation

Table 2. Comparison of first trimester screening serum markers, doppler ultrasonography findings, and urine analysis test results

Variables	Grup I (n=31) Mean ± SD	Grup II (n=76) Mean ± SD	p-value
PAPP-A	1.15±0.53	1.14±0.57	0.9
β-hCG	1.09±0.75	1.02±0.66	0.5
NT (mm)	1.42±0.25	1.40±0.22	0.6
NT (MoM)	0.88±0.14	0.88±0.12	0.9
CRL	63.3±7.2	61.8±6.5	0.1
Right Uterine Artery PI	1.75±0.55	1.77±0.6	0.7
Right Uterine Artery RI	0.74±0.10	0.75±0.09	0.7
Left Uterine Artery PI	1.92±0.69	1.98±0.72	0.5
Left Uterine Artery RI	0.76±0.09	0.78±0.08	0.1
Mean Uterine Artery PI	1.83±0.49	1.88±0.52	0.5
Mean Uterine Artery RI	0.75±0.07	0.76±0.08	0.2
Bilateral Uterine Artery Notch (+)	16 (12.2)	6 (7.9)	0.3
Ketonuria	3 (2.4)	11 (17.2)	<0.01**
Urinary tract infection	37 (29.1)	22 (34.4)	0.4

PAPP-A: Pregnancy-associated plasma protein A, β-Hcg: β-human chorionic gonadotrophin, NT: Nuchal translucency, RI: Resistance-index, PI: Pulsatility-index, CRL: Head-rump distance, SD: Standard deviation, **p<0.05

Table 3. Comparison of demographic characteristics, first trimester screening serum markers, doppler ultrasonography findings

Variables	Grup I (n=131) Mean ± SD	Grup II (n=69) Mean ± SD	Grup III (n=7) Mean ± SD	p-value
Age	29.7±5.0	30.3±4.8	31.3±4.5	0.5
Body mass index (kg/m ²)	24.6±3.7	24.4±3.7	25.9±3.1	0.5
PAPP-A	1.15±0.53	1.14±0.56	1.12±0.68	0.5
β-hCG	1.09±0.75	1.04±0.68	0.88±0.42	0.7
Right Uterine Artery PI	1.75±0.55	1.76±0.58	1.82±0.79	0.9
Right Uterine Artery RI	0.74±0.10	0.75±0.09	0.74±0.11	0.9
Left Uterine Artery PI	1.92±0.69	1.97±0.72	2.08±0.73	0.7
Left Uterine Artery RI	0.76±0.09	0.78±0.10	0.80±0.09	0.3
Mean Uterine Artery PI	1.83±0.49	0.87±0.51	1.95±0.72	0.7
Mean Uterine Artery RI	0.75±0.07	0.76±0.07	0.77±0.09	0.5
NT (mm)	1.42±0.25	1.41±0.23	1.34±0.12	0.6
NT (MoM)	0.88±0.14	0.88±0.12	0.83±0.06	0.6

PAPP-A: Pregnancy-associated plasma protein A, β-Hcg: β-human chorionic gonadotrophin, NT: Nuchal translucency, RI: Resistance-index, PI: Pulsatility-index, CRL: Head-rump distance, SD: Standard deviation

Prior research revealed that high levels of HCG was associated with placentation abnormalities such as preeclampsia, small for gestational age or HG. A population based cohort study involving over one million pregnant women in Sweden also reported that an elevated risk of placentation dysfunction disorders in women with HG. Therefore, uterin artery doppler ultrasonography examination has been suggested in this patient group (13). In a study evaluating first-trimester Doppler ultrasonography findings in pregnant women with HG, it was found that there was no difference in uterine artery Doppler values, except for uterine artery notch (14).

The literature shows contradictory results between HG and first-trimester biochemical markers. Derbent et al. (15) demonstrated that HG was associated with elevated levels of serum maternal PAPP-A and free β-hCG levels. Similarly, Yildiz et al. (16) demonstrated that higher levels of free β-hCG was related to increased risk for HG. However, researchers also noted that no significant relationship was found in uterin artery doppler findings or serum PAPP-A levels. On the contrary, Madendağ et al. (17) found that serum PAPP-A value was significantly decreased in women with HG. But, they also noted that severe HG had no significant effect on free β-hCG levels (17). In this context, we believe that more research needs to be undertaken on this subject in order to better understand the relationship between HG and PAPP-A, and free β-hCG levels.

Another important finding was that this study showed no link between HG and NT. This finding was in line with the suggestion of Yildiz et al. (16), who suggested that there was no relationship between HG and NT.

There are controversies about the association between first trimester uterine artery doppler values and HG. The findings of the current study were consistent with those of Biyik et al. (14) who also found no association between doppler RI, PI, standard deviation (SD) values and HG. In contrast, a recent study by Kartal et al. (18) demonstrated an association between RI, PI, and SD values of the uterine artery Doppler waveform and HG. A possible explanation for this might be that our cohort consisted of outpatients, Doppler and biochemistry values did not differ significantly between groups.

Study Limitations

One of the limitations of the study was the small number of severe HG patients in the study. We believe that the relationship between Doppler and first trimester parameters and HG severity may be elucidated in future large, multi-center studies. To the best of our knowledge, there are many studies on the relationship between first-trimester uterine artery Doppler findings and pregnancy complications, however, there are only a few studies aimed at predicting placentation abnormalities with first trimester uterine artery Doppler in cases with HG.

Conclusion

In our study, no significant relationship was found between the first-trimester uterine artery doppler parameters, biochemical markers and the severity of HG, which was measured according to PUQE scoring system. However, we did find that PUQE test was an effective test in the detection of patients with ketonuria. Further research is needed to better understand the significance of uterine artery Doppler measurements and biochemical markers in cases with HG.

Ethics

Ethics Committee Approval: The study was in line with the Helsinki Decleration and approved the Ethics Committee of the Bezmalem Vakıf University (decision no: 17/22, date: 07.12.2016).

Informed Consent: All participants were informed regarding the study and they gave informed consent prior participation.

Authorship Contributions

Surgical and Medical Practices: M.M., Concept: M.M., İ.A., B.D., Design: M.M., İ.A., B.D., Data Collection or Processing: M.M., E.K., P.Y., M.M.K., R.B.B., E.M., G.Y., İ.A., B.D., Analysis or Interpretation: M.M., E.K., P.Y., M.M.K., R.B.B., E.M., G.Y., İ.A., B.D., Literature Search: M.M., E.K., P.Y., M.M.K., R.B.B., İ.A., B.D., Writing: M.M., E.K., P.Y., M.M.K., R.B.B., E.M., G.Y., İ.A., B.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Hinkle SN, Mumford SL, Grantz KL, Silver RM, Mitchell EM, Sjaarda LA, et al. Association of Nausea and Vomiting During Pregnancy With Pregnancy Loss: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Intern Med* 2016;176:1621-7.
- Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. *J Popul Ther Clin Pharmacol* 2013;20:e171-83.
- Erick M, Cox JT, Mogensen KM. ACOG Practice Bulletin 189: Nausea and Vomiting of Pregnancy. *Obstet Gynecol* 2018;131:935.
- Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Nausea and vomiting of pregnancy: what about quality of life? *BJOG* 2008;115:1484-93.
- Koudijs HM, Savitri AI, Browne JL, Amelia D, Baharuddin M, Grobbee DE, et al. Hyperemesis gravidarum and placental dysfunction disorders. *BMC Pregnancy Childbirth* 2016;16:374.
- Bustos M, Venkataramanan R, Caritis S. Nausea and vomiting of pregnancy - What's new? *Auton Neurosci* 2017;202:62-72.
- Boulanger AS, Paquette I, Létourneau G, Richard-Devantoy S. Thiamine et encéphalopathie de Gayet-Wernicke : quelles règles de prescription ? [Wernicke encephalopathy: Guiding thiamine prescription]. *Encephale* 2017;43:259-67.
- Garg R, Sanjay, Das V, Usman K, Rungta S, Prasad R. Spontaneous pneumothorax: an unusual complication of pregnancy--a case report and review of literature. *Ann Thorac Med* 2008;3:104-5.
- Walch A, Duke M, Auty T, Wong A. Profound Hypokalaemia Resulting in Maternal Cardiac Arrest: A Catastrophic Complication of Hyperemesis Gravidarum? *Case Rep Obstet Gynecol* 2018;2018:4687587.
- Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. *J Obstet Gynaecol Can* 2009;31:803-7.
- Sucu M, Büyükkurt S, Evrûke İC, Demir SC, Özgünen FT, Kadayıfçı O. Gebelikte Bulantı-kusması olan hastaların hastaneye yatış endikasyonlarının değerlendirilmesinde PUQE (pregnancy-unique quantification of emesis and nausea) testinin yeri. *Türkiye Klinikleri J Gynecol Obst* 2009;19:317-21.
- Birkeland E, Stokke G, Tangvik RJ, Torkildsen EA, Boateng J, Wollen AL, et al. Norwegian PUQE (Pregnancy-Unique Quantification of Emesis and nausea) identifies patients with hyperemesis gravidarum and poor nutritional intake: a prospective cohort validation study. *PLoS One* 2015;10:e0119962.
- Bolin M, Åkerud H, Cnattingius S, Stephansson O, Wikström AK. Hyperemesis gravidarum and risks of placental dysfunction disorders: a population-based cohort study. *BJOG* 2013;120:541-7.
- Biyik I, Ocakoglu G, Ustunyurt E, Yılmaz F, Keskin F. Comparison of first trimester uterine artery Doppler parameters in hyperemesis gravidarum with normal pregnancy. *Perinatal Journal* 2016;24:66-71.
- Derbent AU, Yanik FF, Simavli S, Atasoy L, Urün E, Kuşçu UE, et al. First trimester maternal serum PAPP-A and free β -HCG levels in hyperemesis gravidarum. *Prenat Diagn* 2011;31:450-3.
- Yildiz G, Mat E, Kurt D, Yıldız P, Başol G, Gündoğdu E, et al. Hyperemesis Gravidarum and Its Relationship with Placental Thickness, PAPP-A, and Free Beta-HCG: A Case-Control Study. *Southern Clinics of Istanbul Eurasia* 2022;33:406-12.
- Madendağ Y, Çöl Madendağ İ, Eraslan Şahin M, Şahin E, Açmaz G. Effect of Severe Hyperemesis Gravidarum on PAPP-A and hCG in First Trimester. *Bozok Tıp Dergisi* 2019;9:32-5.
- Kartal D, Arıcı Yurtkul A, Şenkaya AR. The role of uterine artery Doppler index and nuchal translucency measurement in predicting perinatal problems and the gestational age in patients diagnosed with hyperemesis gravidarum. *Aegean J Obstet Gynecol* 2020;2:63-6.