

Comparison of first trimester uterine artery Doppler parameters in hyperemesis gravidarum with normal pregnancy

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Abstract

Objective: The purpose of this study was to compare the first trimester uterine artery Doppler measurements between hyperemesis gravidarum (HG), nausea and vomiting of pregnancy (NVP) and control groups.

Methods: In a case-control study, the ratio of bilateral uterine artery pulsatility index (PI), resistive index (RI) and systole/diastole (S/D) were measured transabdominally in 6th to 14th week of gestation of women with hyperemesis gravidarum, nausea and vomiting of pregnancy and normal pregnancy.

Results: A total of 150 cases, consisting of 49 with HG, 51 NVP and 50 normal pregnant women were evaluated. Right and left uterine artery PI, RI, S/D values were found similar between groups ($p>0.05$).

Conclusion: No significant difference was found between HG, NVP and control groups in terms of first trimester uterine artery Doppler parameters in this study. Prospective studies with a large number of cases are required to support our findings.

Keywords: Hyperemesis gravidarum, HG, uterine artery Doppler, first trimester.

Özet: Hiperemesis gravidarumlu olguların ilk trimester uterin arter Doppler parametrelerinin normal gebelerle karşılaştırılması

Amaç: Bu çalışmanın amacı hiperemesis gravidarum (HG), gebeliğin bulantı ve kusması (NVP) ve kontrol grupları arasındaki ilk trimester uterin arter Doppler ölçümlerini karşılaştırmaktır.

Yöntem: Olgu kontrol çalışmasında 6 ve 14 gebelik haftasındaki HG'li, NVP'li ve normal gebelerde transabdominal yolla bilateral uterin arter Doppler pulsatilite indeksi (PI), rezistif indeks (RI), sistol/diastol oranları (S/D) ölçüldü.

Bulgular: Kırk dokuz HG'li, 51 NVP'li ve 50 normal gebe olmak üzere toplam 150 gebe değerlendirildi. Sağ ve sol uterin arter Doppler PI, RI, S/D değerleri gruplar arasında benzer bulundu ($p>0.05$).

Sonuç: Bu çalışmada HG, NVP ve kontrol grupları arasında ilk trimester uterin arter Doppler parametreleri açısından fark bulunmadı. Bulgularımızı destekleyen geniş serili prospektif çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Hiperemesis gravidarum, HG, uterin arter Doppler ölçümü, ilk trimester.

Introduction

Nausea and vomiting of pregnancy (NVP) causes mild nausea and affects 70–85% of pregnant women.^[1] Pregnant women with NVP usually feel better after the first trimester and a negative perinatal effect is not usually

expected. The incidence of hyperemesis gravidarum (HG), a more serious condition, is reported as 0.3 to 3.6%.^[2]

In HG, ketone bodies increase in maternal blood. Increased ketone bodies may cause metabolic acidosis. To provide acid-base regulation in circulation, ventila-

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tion rate increases. Respiratory alkalosis develops with increased ventilation rate. Severe respiratory alkalosis and hypocapnia may cause uterine artery vasospasm, reduced placental perfusion, fetal hypoxia and metabolic acidosis. In such case, uterine artery vascular resistance may increase. Therefore, uterine artery Doppler parameters can be increased. Increased uterine artery vascular resistance may cause placental insufficiency related pregnancy complications.

Some studies report that nausea and vomiting in pregnancy may be related to unwanted results associated with placental insufficiency^[3] while others suggest the opposite.^[4] Some studies carried out to predict pregnancy complications in the first trimester with uterine artery Doppler are reported.^[5] However, there are a limited number of studies where the first trimester artery Doppler measurements have been evaluated in HG.

The purpose of this study was to investigate the relationship between the first trimester uterine artery Doppler measurements used in the prediction of placental deficiency in HG, NVP and control groups.

Methods

This case-control study was carried out in Karacabey State Hospital between January 2014 and September 2015. The Non-Invasive Human Research Ethics Committee of Şevket Yılmaz Training and Research Hospital approved the study. Informed consent was obtained from all cases participated in the study.

Three groups of pregnant women in first trimester from 6 to 14 weeks of gestation were included into the study. First and second groups consisted of women with HG and nausea and vomiting of pregnancy (NVP), respectively. The third one was considered as the control group and consisted of healthy pregnant women without any complaints. The diagnosis of HG was based on the clinical decision as the nausea, protracted vomiting and inability to tolerate food intake accompanied by obvious dehydration severe enough to justify hospitalization with at least 1(+) ketonuria on dipstick urine analysis. NVP was diagnosed when nausea and vomiting was less severe with no history of weight loss and any sign of dehydration, no ketonuria or ketonemia or any other metabolic disorders. The number of cases in the three groups was 49, 51 and 50, respectively.

In the diagnosis of HG, nausea and vomiting, loss of weight, ketonuria, electrolyte abnormalities associated

with vomiting, dry mucous membranes, decreased skin turgor and hypotension findings were considered as the sufficient findings for hospitalization. The pregnant women with nausea which was not severe as much as HG, lasting for the whole day and not associated with ketonuria and loss of weight were established with the diagnosis of NVP. The cases in the control group were chosen among those with healthy singleton pregnancy without full-day nausea.

Those with multiple pregnancies, with a history of hypogastric artery ligation or systemic disease with vascular involvement, and smokers were not included in the study. Those with pyelonephritis or thyrotoxicosis were also not included in the study as these conditions can mimic HG.

The demographic data of the cases such as age, gravida, parity, abortion, and number of living children were recorded. Body analyses such as height, weight, and body mass index (BMI) were recorded. The values of alanine amino transferase (ALT), aspartate amino transferase (AST), urea, blood urea nitrogen (BUN), creatinine, ketonuria, hemoglobin, and thyroid stimulating hormone (TSH) were recorded as laboratory parameters. The gestational week (GA) was recorded in days according to the crown-rump length (CRL) measurement.

We used a 3.5 MHz curvilinear transabdominal transducer for the ultrasound investigation. We first obtained a midsagittal section of the uterus and cervical canal and then moved the transducer laterally until we could visualize the paracervical vessels. Color flow Doppler was used for the session. We visualized the uterine arteries as aliasing vessels along the cervix. Pulsed wave Doppler with the sampling gate set at 2 mm was used to obtain flow velocity waveforms. These waveforms were obtained from the point on the ascending branch of the uterine artery that was closest to the internal os. We used the smallest angle of insonation (< 30°) to obtain the highest systolic and end-diastolic velocities. We measured the PI (pulsatility index), RI (resistive index) and S/D (systole/diastole ratio) when three similar consecutive waveforms were obtained. The presence of a notch in the uterine artery was also investigated. Color flow Doppler and pulsed Doppler durations were kept under a minute for safety during the measurements.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (minimum–maximum) while categorical variables were presented as frequency with the

Table 1. Demographic and laboratory data of the cases.

	Total (n=150)	HG (n=49)	NVP (n=51)	Control (n=50)	p
Age (years)	26.83±5.72	25.76±5.52	27.08±5.48	27.62±6.10	0.251
G	2 (0–6)	2 (0–6)	2 (1–6)	2 (1–6)	0.460
P	1 (0–5)	0 (0–5)	0 (0–3)	1 (0–3)	0.185
A	0 (0–3)	0 (0–2)	0 (0–3)	0 (0–3)	0.522
Y	0.50 (0–4)	0 (0–4)	0 (0–3)	1 (0–3)	0.177
GA (days)	63.50 (41–95)	61 (42–95)	63 (41–91)	64 (41–92)	0.711
Body weight	64.16±13.26	61.28±12.25	66.32±14.67	64.77±12.43	0.153
Height	1.60±0.06	1.59±0.07	1.60±0.06	1.60±0.05	0.654
BMI	25.09±5.32	23.62 (1.62–40.30)	24.60 (18–45)	24.30 (17.30–35.80)	0.362
ALT (IU/L)	12 (6–78)	11 (6–78)	12 (6–58)	13 (6–58)	0.968
AST (IU/L)	16 (7–50)	16 (11–50)	16 (7–34)	16 (10–30)	0.684
Urea (mg/dL)	18.49±5.39	20.65±5.17	18.54±5.05	16.27±5.13	<0.001
Creatinine (mg/dL)	0.62±0.10	0.61±0.06	0.61±0.07	0.63±0.02	0.638
Hemoglobin (g/dL)	12.50 (9–15.40)	12.60 (10.80–15.40)	12.20 (9–14.40)	12.60 (10.20–14.50)	0.314

ALT: alanine amino transferase, AST: aspartate amino transferase, GA: gestational age, BMI: body mass index, HG: hyperemesis gravidarum, NVP: nausea and vomiting of pregnancy

related percentage. The Kruskal-Wallis or ANOVA test was used for between group comparisons whether the variables followed a normal distribution or not. The Bonferroni test was used for multiple comparisons after the ANOVA test. Two group comparisons were performed using the Mann-Whitney U test. The Pearson chi-square test was used for between group comparisons of categorical variables. Statistical analyses were performed using SPSS v.21 (SPSS Inc., Chicago, IL, USA) and the level of significance was set at $\alpha=0.05$.

Results

A total of 150 cases consisting of 49 HG cases, 51 NVP cases and 50 normal pregnancies were evaluated. The demographic data of the cases are presented at **Table 1**. The mean age was 26.83 years, and the mean gestational age 63 days. The mean BMI was 25 kg/m² and the mean

body weight 64 kg. There was no significant difference between the groups in terms of age, gravida, parity, abortion, number of living children, height, body weight, and BMI ($p>0.05$). There was also no significant difference in terms of thyroid stimulating hormone (TSH), ALT, AST, creatinine, and hemoglobin levels ($p>0.05$). Urea levels were higher in the HG group than the control group ($p<0.001$). No significant difference was present for urea levels with the other group comparisons ($p>0.05$).

The mean ketonuria level was 2.02±1.25 (range: 1 to 4) positive in the HG group. The ketonuria level was 1 positive in 26 (53.10%) cases, 2 positive in 7 (14.3%) cases, 3 positive in 5 (10.20%) cases and 4 positive in 11 (22.40%) cases in our HG group.

Uterine artery Doppler parameters of the cases are presented in **Table 2**. No significant difference was found between the groups in terms of PI, RI, and S/D

Table 2. Sonographic findings of cases.

	Total (n=150)	HG (n=49)	NVP (n=51)	Control (n=50)	p
Right UtA PI	2.04±0.55	1.94±0.52	2.14±0.57	2.04±0.55	0.167
Right UtA RI	0.81 (0.16–0.92)	0.80 (0.16–0.91)	0.83 (0.43–0.92)	0.81 (0.49–0.91)	0.053
Right UtA S/D	5.62±2.23	5.24±2.03	6.19±2.51	5.40±2.04	0.072
Left UtA PI	2.16±0.58	2.16±0.54	2.22±0.65	2.08±0.56	0.485
Left UtA RI	0.83 (0.46–0.91)	0.82 (0.55–0.91)	0.83 (0.46–0.91)	0.83 (0.55–0.90)	0.681
Left UtA S/D	5.91±2.24	5.85±0.12	6.18±2.48	5.69±2.12	0.535

HG: hyperemesis gravidarum, NVP: nausea and vomiting of pregnancy, PI: pulsatility index, RI: resistive index, S/D: systole/diastole, UtA: uterine artery

values ($p>0.05$). A notch was present in 81 (54.40%) and absent in 68 (45.60%) cases. The notch information of one case was not recorded. No difference was found between the groups in terms of the notch incidence ($p>0.05$). There was no significant change in the right uterine artery Doppler parameters but the left uterine artery PI, RI, and S/D values decreased as maternal weight and BMI values increased ($p=0.015$, $p=0.033$, $p=0.021$ and $p=0.017$, $p=0.044$, and $p=0.016$, respectively). There was no change in the left uterine artery Doppler parameters but the right uterine artery RI value decreased as the ketonuria increased ($p=0.037$). No significant relationship was found between notch positivity and the ketonuria level ($p>0.05$). No significant relationship was found between the ketonuria level and the TSH, ALT, and AST values ($p>0.05$). The urea value increased as the ketonuria level increased (<0.001).

Discussion

Ketone bodies are water-soluble molecules that are produced by the liver from fatty acids during periods of low food intake (fasting) or carbohydrate restriction for cells of the body to use as energy instead of glucose. The three endogenous ketone bodies are acetone, acetoacetic acid, and beta-hydroxybutyric acid. When ketone bodies increase in maternal blood, ventilation rate increases to provide acid-base balance. Severe respiratory alkalosis and hypocapnia may cause uterine artery vasospasm, reduced placental perfusion, fetal hypoxia and metabolic acidosis.^[6] In such case, uterine artery vascular resistance may increase. Therefore, uterine artery PI, RI and S/D values may elevate.

Nausea and vomiting are common problems in pregnancy. NVP usually improves after the first trimester of pregnancy and is usually not associated with adverse pregnancy outcomes. However, the reports on the outcomes of pregnancy with HG, the most severe form of nausea and vomiting, are conflicting. NVP generally recovers after the first trimester and it is usually not associated with adverse pregnancy outcomes. On the other hand, gestational outcomes in HG are controversial. In this study, we investigated the relationship between the first trimester uterine artery Doppler measurements used in the prediction of placental deficiency in HG, NVP and control groups.

Some studies suggest that HG does not cause adverse pregnancy outcomes.^[7-11] Other studies suggest

that HG is associated with adverse pregnancy outcomes. Some studies have reported that limitation in weight gain due to HG in pregnancy increased the risk of SGA (small-for-gestational age) and preterm birth.^[3,12,13] More recently, Bolin et al. reported with a large population study in Sweden that pregnancies with HG had a slightly increased risk of preeclampsia, and especially preterm preeclampsia compared with pregnancies without HG. They also found that pregnancies with HG were associated with an almost 50% increased risk of placental abruption and a slightly increased risk of an SGA birth compared to the other group. The early onset preeclampsia risk was also increased in the women with HG. The authors believed that early onset preeclampsia in particular may be related to inadequate spiral artery remodelling and HG may be related to placental deficiency. They recommended a study to be conducted to evaluate HG cases with uterine artery Doppler.^[14] Roseboom et al. concluded that adverse pregnancy outcomes were more prevalent among women who had suffered from HG. This group more often delivered prematurely and more often had a baby that was small for gestational age.^[15] Vikanes et al. reported that HG was associated with a decreased risk for delivering a child with a 1-minute Apgar score <7 , but no difference was observed in 5-minute score.^[16]

Several studies aiming to predict pregnancy complications such as preeclampsia, low birth weight, and preterm birth in the first trimester have been conducted in recent years. These studies have focused on the prediction of placental deficiency with uterine artery Doppler measurements and biochemical markers. Some studies report that high uterine artery Doppler PI values reflect placental deficiency.^[17] Many studies have tried to predict pregnancy complications related to abnormal placentation (preeclampsia, IUGR, low birth weight, etc.) with first trimester uterine artery Doppler evaluations. Poon et al. reported that mean arterial pressure and the lowest 11–14 week uterine artery PI values increased and pregnancy-associated plasma protein A (PAPP-A) decreased in preeclampsia compared to the controls. The risk of delivering an SGA fetus was found to be high in pregnant women with high first trimester PI values in some studies.^[18,19] There are many studies on detecting pregnancy complications with first trimester uterine artery Doppler but only a few studies aiming to predict placental deficiency with first trimester uterine artery Doppler in cases with HG.

First trimester PAPP-A levels have been found to be low in pregnancies complicated with preeclampsia, SGA and preterm birth in some studies.^[20–22] Derbent et al. found higher PAPP-A levels in their HG cases than the control group.^[23]

We compared the uterine artery parameters of the HG, NVP and control groups in this study. No significant difference was found between the three groups in terms of first trimester uterine artery Doppler PI, RI, and S/D values. The lack of a difference in the PI value that reflects placental deficiency supports the findings of Derbent et al.^[23] The PAPP-A value is found to be low in placental deficiency situations. However, Derbent et al. found the PAPP-A value to be high in the HG group.^[23] The lack of a difference in PI values between the three groups indicates that the placental deficiency risk in HG may not be high. There are also other studies that support our opinion.^[8–10] However, it is possible that no difference was found because the uterine artery Doppler was performed in the early first trimester (an average of nine weeks) in this study. It would have been possible for us to answer the question of whether abnormal Doppler findings appear later on or not at all in HG cases if we knew the pregnancy outcomes. However, the limited number of cases and the fact that the pregnancy outcomes were not known are the limitations of our study. We therefore believe that studies with large series evaluating first and second trimester uterine artery Doppler in HG cases with the pregnancy outcomes may be useful.

Conclusion

In conclusion, we found no significant difference between HG, nausea and vomiting of pregnancy and control groups in terms of uterine artery Doppler parameters in this study. Prospective studies with a large number of cases where the birth data were registered are required to support our findings.

Conflicts of Interest: No conflicts declared.

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