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Original Article

The role of uterine artery Doppler indices in predicting pregnancy complications in hyperemesis gravidarum

Dilek Kartal [a], Azra Arıcı Yurtkul[a], Ayşe Rabia Şenkaya [a, †]

[a] *Department of Obstetrics and Gynecology, University of Health Sciences Tepecik Training and Research Hospital, İzmir, Turkey*

ABSTRACT

Objective: We aimed to investigate the effectiveness of uterine artery Doppler index and nuchal translucency (NT) measurement in determining perinatal problems in patients diagnosed with hyperemesis gravidarum (HEG).

Material and methods: We included 80 pregnant women between the ages of 19–40 years with a singleton, noncomplicated pregnancy, no systemic disease, and no structural and chromosomal disorders in the fetus, who were admitted to our hospital which is a tertiary center with a large patient population in the region, between October 2015 and October 2016 in this study. Further, two group were formed as 40 pregnant women with the diagnosis of HEG (group 1) and 40 pregnant women for control group (group 2). Age, body mass index (BMI), educational status, pregnancy history (live birth, miscarriages), smoking, alcohol consumption, substance use, last menstrual period, serum pregnancy-associated plasma protein A (PAPP-A), free beta-human chorionic gonadotropin, (free ß-hCG), thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) levels, nuchal translucency (NT), and uterine artery Doppler measurement values were recorded. The data between two groups were compared.

Results: The education level of the group 1 was found higher (p = 0.001). The frequency of smoking in group 1 (n = 18; 45%) was found significantly higher than group 2 (n = 3; 7.5%) (p = 0.001). In group 1, uterine artery Doppler pulsatility index (PI) and resistance index (RI) values were found higher than group 2 (p = 0.026 and 0.024, respectively).

Conclusion: The uterine artery Doppler PI, RI values measured at 20–24 weeks in patients with HEG were statistically significantly higher than those without HEG.

Keywords: doppler; hyperemesis gravidarum, pregnancy, uterine artery

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Introduction

Nausea and vomiting during pregnancy that occur during the early pregnancy weeks usually is experienced in the morning and is seen in 50%–90% of pregnancies.[1] Although this nausea and vomiting usually disappear at the end of the first trimester, sometimes it persists in the second trimester as well.[2]

Hyperemesis gravidarum (HEG) is seen in approximately 0.2%–2.3% of pregnancies with nausea and vomiting.[1], [2]

Diagnostic criteria about HEG is nearly the same in the literature. Sometimes, acid-base disorder, electrolyte imbalance, dehydration, ketonuria, weight loss, and at times hepatic and renal failure can be seen in patients. It is characterized by persistent nausea and vomiting that may require hospitalization.[3], [4]

The etiopathogenesis of HEG has not been fully elucidated. Metabolic and hormonal changes, immunological factors, gastrointestinal system dysmotility, and psychological factors have been emphasized in the etiology, but none of them has been clearly proven to be effective.

Some studies report that nausea and vomiting in pregnancy may be related to unfavourable results associated with placental insufficiency while others suggest the opposite.[5], [6]

Some studies carried out to predict pregnancy complications in the first trimester with uterine artery Doppler are reported.[7]

However, there are a limited number of studies where the first trimester artery Doppler measurements have been evaluated in HEG. Doppler USG is an important auxiliary diagnostic method in detecting fetal distress in high-risk pregnant women with intrauterine growth restriction (IUGR) and preeclampsia.

In this study, we aimed to investigate the effectiveness of uterine artery Doppler index and nuchal translucency (NT) measurement in determining perinatal problems in patients diagnosed with HEG.

Material and methods

80 pregnant women between the ages of 19–40 years with a singleton, noncomplicated pregnancy, no systemic disease, and no structural and chromosomal disorders in the fetus, who were admitted to our hospital which is a tertiary center with a large patient population in the region, between October 2015 and October 2016 included in this study. Two group were formed as 40 pregnant women with the diagnosis of HEG (group 1) and 40 pregnant women for control group (group 2). A weight loss of ≥5% in patients without known gastrointestinal system or psychiatric disease for the diagnosis of HEG were sought for the

† Corresponding author.
E-mail: dr.aysekanbak@gmail.com
ORCID ID: 0000-0003-1538-6965,

presence of at least one positive ketone in the urine test, signs of acid-base disturbance, electrolyte imbalance, or hepatic and renal insufficiency in addition to the severe nausea and vomiting. Detailed information was given to the patients about all procedures and their written consent was obtained. The study was approved by the Human Ethics Committee (ANNEX-1).

Uterine Artery Doppler Measurement

Of note, all pregnant women were allowed to rest for at least 15 minutes before the measurement. Doppler USG was performed in the semi recumbent position. Doppler waveforms were obtained by the same obstetrician. All sonographic measurements were performed transabdominally using a 5 MHz convex abdominal probe (Samsung Medison-Accuvix A30). NT measurement at 11–14 weeks and bilateral uterine artery Doppler measurement at 20–24 weeks were measured. For uterine artery Doppler, the USG probe was placed such that the sagittal section of the uterus and cervical canal was viewed. The uterine arteries were visualized with color Doppler USG by tilting the transducer slowly. The RI, PI, and S/D values of the right and left uterine artery were measured by applying pulse-wave Doppler at the closest point to the branches of the uterine arteries near the internal ostium by obtaining five similar waves. Notching appearance in the waveform, end-systole, or early diastole was defined as notching, as in the literature.

Biochemical Analysis

Serum pregnancy-associated plasma protein A (PAPP-A), free beta-human chorionic gonadotropin (free ß-hCG), and thyroid function test values were measured between 11–14 weeks of pregnancy. Hormone levels were studied in the Immulite 2000 xpi device with the chemiluminescence method.

Evaluation of Patients

Age, body mass index, educational status, pregnancy history (live birth-miscarriage numbers), smoking, alcohol consumption, substance use, last menstrual period, PAPP-A, free ß-hCG, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) levels, NT, and uterine artery Doppler measurement values were recorded.

The pregnant women included in the study were followed up until delivery, and the following complications were recorded during these follow-ups: preeclampsia, fetal growth restriction, intrauterine fetal death, premature birth, cesarean section delivery due to fetal distress, low birth weight, neonatal intensive care need, and neonatal mortality.

The body mass index was calculated according to the kilogram/height (m^2) formula. The overweight limit was accepted as 25 kg/m^2 and above.

Infants with a birth weight below the 10th percentile according to gestational age were defined as low birth weight and preterm delivery before 37 weeks of gestation

Statistical analysis

The data were recorded in SPSS (Statistical Package for Social Sciences) for Windows, version 16.0 (SPSS Inc. Chicago, IL, USA, 2006), and statistical analysis was performed. The morbidities observed with demographic data, laboratory parameters, and Doppler index findings of the pregnant women were given as n (%) or mean ± standard deviation (lower-upper value), according to the appropriate method. The compatibility of numerical values to normal distribution was evaluated with the single sample Kolmogorov–Smirnov test. Numerical data showing normal distribution between groups were compared using independent group Student's t-test. Numerical data and ordinal data not showing normal distribution were compared using the Mann–Whitney U test. Chi-Square or Fischer tests were used to compare rates between groups. Statistical evaluation of $p < 0.05$ was considered significant.

Results

We included 40 participants for HEG (group1) and 40 participants for control group (group 2). Demographic variables, NT, PAPP-A, free ß-hCG, TSH, fT3, fT4 values of the pregnant women included in study are given in Table 1.
It was found that the education level of the group with HEG was higher ($p = 0.001$). The frequency of smoking in the group with HEG was found statistically higher ($p = 0.001$).
Nuchal translucency, PAPP-A, and free βhCG values of participants were found similar ($p = 0.796$, $p = 0.911$, $p = 0.140$, respectively).
The median values of TSH (1.3 mU/L and 1.8 mU/L, respectively) were compared, it was found that the TSH value was much more suppressed in the group 1. However, this did not reach statistical significance ($p = 0.054$). The fT3 values were similar ($p = 0.260$) and free T4 values were found to be higher in the group 1 ($p = 0.001$).
When the correlation of TSH with free βhCG was evaluated, it was found that these two laboratory parameters did not correlate ($r = 0.160$, $p = 0.156$). In addition, while there was no correlation between TSH and fT3 and fT4, a weak positive correlation was found between fT3 and fT4 ($r = 0.243$, $p = 0.030$).
While a total of 15 pregnant women (18.8%) received thyroid-related treatment in the follow-up, 11 of them (27.5% of the patients with HEG) were in the group 1 and receiving thyroid-related treatment in the group 1 was higher ($p = 0.045$).

Table 1. Demographic characteristics of groups with and without HEG, NT, fβhCG, PAPP-A, TSH, fT3 and fT4 values

	Group 1 (n,40)	Group 2 (n,40)	P value
Age (year)	25,7±5,3	27,4±4,6	0,130
Height (cm)	159±14	161±6,0	0,251
Weight (kg)	70,6±18,4	69,2±12,9	0,690
Body Mass Index (kg/m^2)	26,5±4,5	26,6±4,6	0,933
NT (mm)	1,2±0,4	1,2±0,3	0,796
PAPP-A (MoM)	1,0±0,5	1,0±0,6	0,911
fβhCG (MoM)	1,0±6	1,3±0,9	0,140
TSH (mU/L)	1,8±1,7	2,4±2,3	0,054
fT3 (pg/ml)	3,0±0,5	3,1±0,4	0,266
fT4 (pg/dl)	1,2±0,4	0,9±0,2	*0,001*

HEG: hyperemesis gravidarum, NT: nuchal translucency, PAPP-A: pregnancy-associated plasma protein A, MoM: multiple of median, fβhCG: free beta human chorionic gonadotropin, TSH: thyroid stimulating hormone, fT3: free tri-iodothyronine, fT4: free thyroxine.

Doppler USG was applied to all patients and PI, RI, and S/D values were measured. Doppler measurement values of the pregnant women included in the study are given in Table 2.
Doppler PI and RI values in the group 1 were higher group 2 and this was statistically significant ($p = 0.026$ and 0.024, respectively). Doppler S/D values in the group 1 were found to be similar to group 2 ($p = 0.096$).
When the groups 1 and 2 were compared in terms of notching, 9 (22.5%) of the group 1 and 4 (10%) of the group 2 had notching.
There was no statistical difference between the two groups in terms of notching frequency ($p = 0.130$).
There was no statistical difference between the two groups in terms of preeclampsia frequency ($p = 0.130$). Preterm

labor occurred in 7 pregnant women (8.8%). Six of these 7 pregnant women had no HEG findings. The frequency of preterm labor was higher in the group 2 than in the group 1 (p = 0.048).

Table 2. Doppler PI, RI and S / D values in pregnant women with HEG and without HEG

	Group 1 (n,40)	Group 2 (n,40)	P value
Doppler PI	1,4±0,9	1,0±0,6	0,026
Doppler RI	0,7±0,3	0,6±0,2	0,024
Doppler S/D	2,7±1,2	2,4±0,3	0,096

HEG: hyperemesis gravidarum, PI: pulsatility index, RI: resistive index, S/D: systole/diastole

There were 38 (47.5%) cesarean sections, frequency of cesarean section and cesarean section indications in pregnant women with and without HEG was found to be similar (p = 0.654 and p = 0.205).

The frequencies of small for gestational age (SGA) and intrauterine growth restriction (IUGR) were similar in the groups 1 and 2 (p = 0.166 and p = 1,000, respectively).

The pregnant women with only HEG were taken and the factors that could affect the frequency of cesarean section due to IUGR, SGA, preeclampsia, preterm labor, and fetal distress were investigated.

Discussion

Nausea and vomiting occur in 70%–80% of pregnancies. However, HEG occurs when dehydration, liquid electrolyte abnormalities, and weight loss add to the picture.[8]

HEG can cause several maternal complications. If left untreated, fetal complications can be serious and infant death can also occur. Hydration, antiemetic drugs, and enteral or parenteral nutrition can be used in the treatment of HEG. Fetal complications are expected to be minimal in patients with HEG who receive treatment under these conditions. In patients with HEG who receive treatment, there is a lesser frequency of premature births or birth defects, and a good maternal and fetal prognosis; however, low birth weight is observed. [9], [10]

In this study, our aim is to investigate the role of 1st trimester prenatal tests and 2nd trimester uterine artery Doppler measurements in predicting pregnancy outcomes in patients with hyperemesis gravidarum.

Studies on pregnancy outcomes in patients with HEG are controversial. In a study conducted by D Paauw et al. in 2005 on 45 patients with HEG, they found that fetal weight and gestational age decreased in pregnancies with HEG.[11] Tierson and Hallak could not find a relationship between HEG and fetal weight in their studies.[10], [12] In the studies of Lao et al. they determined that HEG had a negative effect on fetal weight.[13] In 2007, Maconochie et al. stated that fetal loss and preeclampsia risk is low in pregnancies complicated with HEG, but the risk of preterm birth, low birth weight, and low APGAR score is high.[14] In 1996, Hallak et al. stated that HEG did not increase the risk of IUGR and prematurity.[10] In 2006, Dod's et al. found that the rate of low birth weight and preterm delivery was higher than the control group.[5] In our study, the two groups were similar in terms of mean birth weight. The average age of the group 1 and group 2 was similar.

The mean gestational age of the groups with and without HEG was similar. The reason why the results of both groups were similar in our study may be that a small number of patient populations were included in the study.

In 2011, Derbent et al found the median PAPP-A MoM value to be higher in patients with HEG (p = 0.009). Similarly, the median free βhCG value in patients with HEG found as 1.3 MoM which is higher than the control group (p = 0.006).[15] In our study, NT, PAPP-A, and free βhCG values of the two groups were found to be similar.

There are various studies in the literature on hyperemesis gravidarum and thyroid functions. Rodien et al. showed in 2004 that the increase in hCG levels increases thyrotropic activity.[16] Goodwin et al. in 1992 showed that TSH was suppressed in 70% of patients with HEG. Thyroxine levels were correlated with hCG levels. They stated that the role of hyperthyroidism in patients with HEG was not clearly understood.[17] Leunen M et al. detected 22.9% of hyperthyroidism in 48 pregnant women with hyperemesis and stated that antithyroid therapy in these patients not only normalized thyroid tests but also provided a significant improvement in the HEG symptoms. As a result of this study, they stated that the degree of thyroid stimulation did not affect the severity of the disease and the outcome of pregnancy.[18]

In our study, the median values of TSH in the groups 1 and 2 did not comply with the normal distribution, and it was found that the TSH value was more suppressed in the group with HEG. However, this did not reach statistical significance. The fT3 values were similar in the groups 1 and 2. Free T4 values were found higher in the group 1 than in the group 2. Studies have found that there is a significant correlation between the increase in RI, PI, and S/D values of the uterine artery Doppler waveform and the presence of early diastolic notching, preeclampsia, and poor pregnancy prognosis.[19] In the study conducted by Bıyık et al. In 2016, normal pregnant women, pregnant women with vomiting and pregnant women with hyperemesis gravidarum were compared in three groups. There was no difference between the groups in terms of uterine artery Doppler measurements.[20]

In our study, uterine artery Doppler PI and RI values in the group 1 were found to be higher than the group 2 and this was statistically significant. This result shows the importance of uterine artery Doppler measurement in pregnant women with hyperemesis gravidarum.

Doppler S/D values in the group 1 were found to be similar to the group 2. When the groups 1 and 2 were compared in terms of notching, 9 (22.5%) of the group 1 and 4 (10%) of the group 2 had notching. Both groups were statistically similar in terms of notching frequency. The frequency of preterm labor was found to be higher in the group 2 than the group 1. It was observed that this situation did not conform to the literature and it was thought that the reason might be that pregnant women with HEG were followed up more closely. When groups 1 and 2 were compared in terms of cesarean section indications due to fetal distress by taking only cesarean section pregnancies, it was found to be similar. SGA and IUGR frequencies were similar in groups 1 and 2.

The fact that our study is prospective and case-controlled is a valuable aspect of our study. The limitation of our study is that a small number of patients were included in the study.

During the initiation of hospitalization in patients with hyperemesis, the underlying causes should be investigated and treatment options should be individualized for each patient. According to the results of our study, it was thought that adding uterine artery Doppler measurement to antenatal screening tests, especially between 12–14 weeks and 20–24 weeks, by performing two evaluations during pregnancy follow-up would be beneficial in predicting adverse pregnancy outcomes.

Maternal and fetal complications can be reduced with more effective management of high-risk pregnant women.

We are of the opinion that this idea should be supported by studies employing more number of cases.

Disclosure

Authors have no potential conflicts of interest to disclose.

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