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ORIGINAL ARTICLE

Is There a Relation Between Chorion Frondosum Thickness and Severe Hyperemesis Gravidarum?

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Abstract

Background: Hyperemesis gravidarum (HG) is a pregnancy complication that is characterized by severe nausea, vomiting, weight loss, and dehydration. The current study investigated chorion frondosum (CF) thickness and the relation between placental dysfunction and hyperemesis gravidarum.

Methods: We enrolled 96 participants in this study during their first trimester of pregnancy. We found that 48 of them had hyperemesis gravidarum symptoms and +2/+3 urine ketone levels. The others were taken as controls. Demographic characteristics, blood β-hCG, thyroid hormone levels (TSH, fT3, fT4), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and urine ketone levels were obtained from all participants. The CF thickness of each participant was measured to demonstrate the relation between CF thickness and HG.

Results: The mean gestational age was 8.69 (± 2.15) weeks in the HG group and 8.92 (±2.14) weeks in the control group ($p=0.6$). The HG group had significantly higher urine ketone levels (+2.7) compared to the control group (+0.1) ($p<0.001$). The CF thickness was significantly higher in the HG group (16.02 mm) than in the control group (13.50 mm) ($p=0.02$).

Conclusion: The mean chorion frondosum thickness (CF) was significantly higher in the HG group than the healthy controls. This finding may also constitute clinical prediction, in addition to indicating pathophysiology.

Keywords: Chorion; hyperemesis gravidarum; ultrasonography.

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INTRODUCTION

Hyperemesis gravidarum is a pregnancy-specific clinical condition with nausea and vomiting and it can cause critical weight loss and ketoacidosis in severe cases. The incidence of hyperemesis gravidarum (HG) is 0.3-1.5% of all pregnancies (1). Although emesis gravidarum is a common and pregnancy-specific finding in the Turkish population, HG is the most common reason for hospitalization in the first trimester (2). Women with hyperemesis gravidarum have an increased risk for small gestational age (SGA) as shown in a recent meta-analysis (3). This can be evaluated as a demonstration of the correlation between placental disorders and hyperemesis gravidarum. An abnormal placenta or an abnormal placenta location is related to poor obstetric outcomes like small for gestational age, pre-eclampsia, placental abruption, and stillbirth (4–6). One of the theories is that increased β-hCG levels are caused by inadequate trophoblast invasion and subsequent placental hypoxia (7). There is a relation between imperfect placentation, compensatory growth, and an increased number of pregnancy complications that were linked to HG pathophysiology (8). Besides, there is a positive correlation between β-hCG levels and nausea and vomiting during pregnancy (9). Higher β-HCG levels present as HG in early pregnancy. Later, it occurs as preeclampsia (PE) and early neonatal complications (8). The effects of placental weight on placental function in hyperemesis gravidarum patients were previously investigated and a correlation between a heavy placenta compared to birth weight has been proven (10). Considering the mentioned literature, the present study started with the hypothesis that placental dysfunction is related to hyperemesis gravidarum. According to our hypothesis, this relation affects chorion frondosum (CF) thickness. The current study aimed to reveal the relationship between CF thickness and HG.

MATERIALS AND METHODS

This prospective clinical study with a parallel design was conducted in a tertiary referral center between February 2023 and June 2024. Inclusion criteria were determined as being in the first trimester of pregnancy and having a diagnosis of hyperemesis gravidarum for the study group. Healthy pregnant women who applied to the outpatient clinic in the first trimester of pregnancy were included in the control group. Exclusion criteria were a history of hyperthyroidism, type 1 diabetes mellitus, positive urine culture test, early pregnancy bleeding, smoking, and an elevated liver function test, as they may cause nausea and vomiting or affect urinary ketones, and CF thickness and affect study homogeneity. In the current study, the definition of HG was made as moderate and severe nausea and vomiting accompanied by ketonuria, seen in the first trimester of pregnancy. Based on previous data, we calculated that for a power of 80% and significance of 5%, by taking impact size 1,02, a minimum sample of 46 patients for both groups was required. Taking into consideration possible dropouts, we enrolled 96 participants in the trial (11).

Age, body mass index (BMI), gravida, parity, pregnancy week, and hyperemesis history in prior pregnancy were obtained from the participants at admission. For laboratory tests, blood β-hCG, thyroid hormone levels (TSH, fT3, fT4), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urine ketone levels, and urine culture were checked for all participants at admission. Participants who had a history of hyperthyroidism and high AST or ALT levels were excluded from the study.

Ultrasonographic examinations were performed by the same experienced physician (C.S.) for all patients to prevent the intra-observer difference in measurements. Ultrasonographic examinations were performed using a Voluson E8 ultrasound machine (GE Healthcare, UK) with a Rab 4-8d 4D probe (GE Healthcare, UK). The CF thickness of each participant was measured. The CF thickness, in mm, was measured at the central thickest area. The myometrial and sub-chorionic veins were excluded from the measurement, and all the chorionic measurements were taken during the relaxed phase of the uterus as contractions can suddenly increase the CF thickness. To ensure standardization, three measurements were taken from the thickest part of the CF in the vertical position of the uterus and the average value was recorded (Fig. 1).

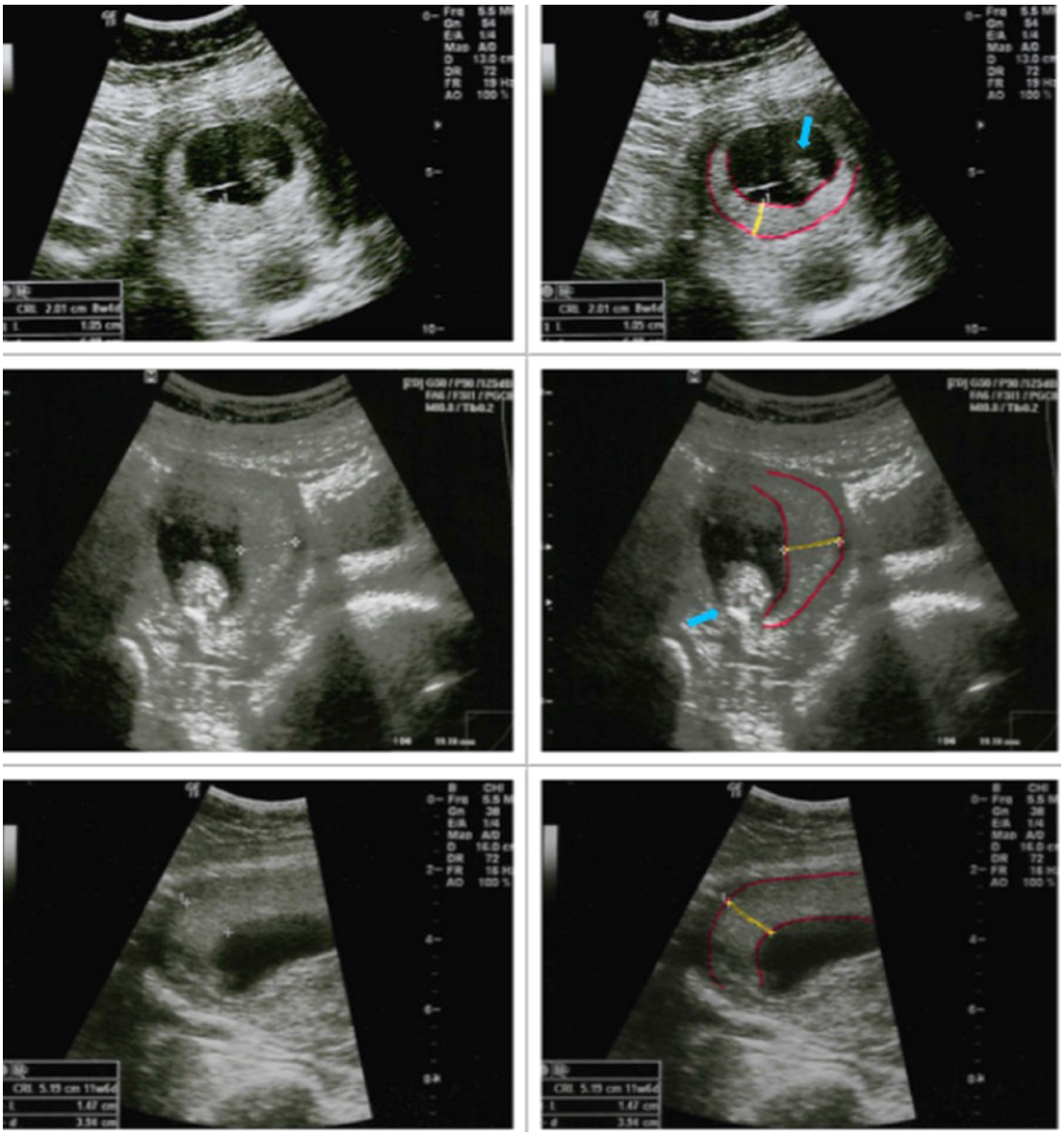

Fig. 1: Measurement of Chorion frondosum (CF) technique. Area of between red lines: CF, Yellow line: CF thickness, Blue arrow: Embryo

Statistical Analyses

The Kolmogorov-Smirnov normality test was used to evaluate the normal distribution of the numeric variables. The mean of normally distributed variables (CF thickness, body mass index (BMI), fT3, fT4, and β-hCG results) was compared using the unpaired t-test, the non-normal distributed variables (rest the of variables) were compared using the Mann-Whitney U test. The Spearman Correlation coefficient was calculated to examine the correlation between the data. p-value < 0.05 were considered statistically significant Statistical analyses were performed using GraphPad Prism version 7.00 (La Jolla, CA, USA).

The local ethics committee of Izmir Bakircay University approved the trial with 865 reference IDs. Written informed consent was obtained from all participants. All procedures performed in the current study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS

We enrolled 96 participants who were admitted to our outpatient clinic in their first trimester of pregnancy. A total of 48 participants with hyperemesis gravidarum symptoms and +2/+3 urine ketone levels were enrolled in the study group and 48 healthy pregnant women in the first trimester of pregnancy were enrolled in the control group.

There were no statistically significant differences between the groups in demographic variables (Table 1). The mean gestational age was 8.69 (± 2.15) weeks in the HG group and 8.92 (±2.14) weeks in the control group. There was no statistical difference between the two groups in terms of gestational age (p=0.6). There were 27 patients in the HG group who had HG during a prior pregnancy while only 4 participants in the control group did, providing evidence of its tendency to repeat. It was found that nausea and vomiting started at 6 weeks and 6 days on average for the HG group, and 19 patients had to be hospitalized for treatment during the study period. The symptoms tended to end at the 18th week of pregnancy.

Table 1. Demographic data

	HG Group (mean) (n=48)	*Control Group (mean) (n=48)*	*p Value*
Age	27	25,7	p>0,05
BMI (kg/m2)	24,6	23,84	p>0,05
Pregnancy	1,95	2,29	p>0,05
Parity	0,75	0,85	p>0,05

Urine ketone levels were +2.7 in the HG group but +0.1 in the control group. The HG group had significantly higher urine ketone levels compared with the control group (p<0.001). The HG group's mean TSH levels were determined as 0.99 mU/L, and the control group's mean TSH level was 1.57 mU/L. Mean AST and ALT levels in HG were 19.69 to 19.65 U/L and for the control group, they were 18.22 to 18.22 U/L, respectively. There was no statistical difference between groups in terms of blood AST and ALT levels. TSH was significantly suppressed in the HG group (p=0.0019) but the differences in the fT3 and fT4 levels were not significant between the groups (p=0.07, p=0.49, respectively) (Table 2).

Table 1. Demographic data

	HG Group (mean) (n=48)	*Control Group (mean) (n=48)*	*p Value*
Age	27	25,7	p>0,05
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Pregnancy	1,95	2,29	p>0,05
Parity	0,75	0,85	p>0,05

Ultrasound examination revealed the mean CF thickness was 16.02 mm in the HG group. Conversely, the mean CF thickness was 13.50 mm in the control group. The CF thickness was significantly higher in the HG group than in the control group (p=0.02) (Table 2). Blood Blood-hCG values were also higher in the HG group following the CF thickness at 109620 mlU/ml in the HG group and 99201 mlU/ml in the control group. However, statistical significance was not achieved between the groups in terms of β-hCG levels (p=0.34).

DISCUSSION

Nausea and vomiting were seen as synonymous with the onset of pregnancy. The severity of nausea and vomiting is correlated with β-hCG levels and peaks in the 9th week of pregnancy (12). A diagnosis of hyperemesis gravidarum can be mentioned in cases where the pregnant woman's happiness about the relation between nausea/vomiting and a desired pregnancy is disrupted. Although the etiology of HG is cloudy, it is obvious that the quality of life of pregnant women is significantly decreased by HG (1,13,14). The current study was designed to compare CF thickness between women with HG and healthy controls. Based on our findings, we showed that the mean chorion frondosum thickness (CF) was significantly higher in the HG group compared to the controls. Literature is scarce on the relation between CF thickness and HG. However, researchers proved the link between insufficient placentation, HG, and the compensatory growth of the placenta.

Despite the cause of HG being unknown, its results have been extensively investigated. Bolin et al. showed an association between placental dysfunction and HG via a very large population-based cohort study. According to their research, HG cases in the first trimester had an increased risk of pre-eclampsia. Additionally, in cases presented in the second trimester with HG symptoms, the risk of preterm pre-eclampsia and placental abruption was increased two- to three-fold. These patients also had an increased risk for a small for gestational age birth (15). According to Bolin; HG and high β-hCG levels could be a compensatory mechanism for insufficient placentation. In an observational study, Ali et. al. showed that there was an association between low birth weight with HG. According to their study, there was an increased frequency of term-SGA, and preterm-SGA births in the HG group (8). Our findings are consistent with this study that concluded abnormal placentation may cause hyperemesis gravidarum (15). Thus, hyperemesis gravidarum and increased CF thickness, might be an early pregnancy indicator of a process that results in symptomatic placental dysfunction later. A relationship between low birth weight and HG was also demonstrated in a prospective cohort study with 2252 pregnant participants in Indonesia. However, in that study, they did not find any differences in terms of other placental functional disorders or poor neonatal outcomes (11).

Women with severe HG have a reduced caloric intake and lose nutrients and electrolytes (10). As a result of this, HG often involves ketonuria, which is frequently tested by physicians (9). We found that the HG group had significantly higher urine ketone levels compared with the control group, like the literature.

On the other hand, data indicating that the placental weight reflects the function of the placenta has provided new opportunities in daily practice (16,17). As a result of many observations, clinicians have concluded that maternal undernutrition causes increased placental weight but a decreased birth weight. Despite the inadequate nutrients, the compensatory growth of the placenta presents an explanation for maintaining the necessary nutrient transfer (18). In addition, prior trials have shown that placental efficiency changes in women who are exposed to famine. During the Dutch famine of 1944-45, pregnant women had increased placental weight which suggests compensatory growth where nutrients are inadequate (19). The same compensator mechanism might occur in women with severe hyperemesis gravidarum (11). Vandraas et al. also confirmed that HG has been associated with a high placental weight/birth weight (PW/BW) ratio in another large population-based study. However, the extent of the high PW/BW ratio was limited for women with female fetuses in their trials (10). Compensatory growth of the placenta in women with severe HG might result in increased CF thickness in accordance with our data. However, the explanation for this finding remains unclear.

The strengths of this study are its cross-sectional design and the performance of all the ultrasonic measurements by the same experienced physician to avoid inter-operator variability and bias. Additionally, three measurements were taken for all participants, and the average value was recorded for the standardization of ultrasonographic examinations. However, lack of follow-up for infants is a limitation of the study.

The main new finding of the present study is that the mean CF thickness was significantly higher in the HG group than in the control group. After that, studies can be conducted to express how CF thickness can be used in diagnosing and staging HG.

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Abbreviations list

HG: Hyperemesis gravidarum
CF: Chorion Frondosum
AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
SGA: Small for Gestational Age
BMI: Body Mass Index

Ethics approval and consent to participate

The local ethics committee of Izmir Bakircay University approved the trial with 865 reference IDs. All procedures performed in the current study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Written informed consent was obtained from all participants.

Availability of data and materials

Data related to the study is not stored digitally.

Competing interests

The authors declared no conflict of interest.

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Authors' contributions

Idea/Concept: CS Design: SAA, CS. Control/Supervision IK. Data Collection And/or Processing: SAA, CS, IK. Analysis And/or Interpretation: IK. Literature Review: SAA. Writing The Article: SAA. Critical Review: CS, IK.

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