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Original Article

Hyperemesis Gravidarum and Its Relationship with Placental Thickness, PAPP-A, and Free Beta-HCG: A Case–Control Study

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ABSTRACT

Objective: The aim of this study was to evaluate the relationship of hyperemesis gravidarum (HG) with placental thickness, pregnancy-associated plasma protein-A (PAPP-A), and free beta-human chorionic gonadotropin (beta-HCG) levels.

Methods: A total of 263 pregnant women (93 with HG and 172 controls) who applied to the gynecology and obstetrics outpatient clinic for a combined test between 11 and 14 weeks of gestation were included in this study. Crown-rump length (CRL, measured in millimeter) values were measured using ultrasonography, and PAPP-A and free beta-HCG values (MoM) were recorded from laboratory reports.

Results: The placental thickness ($p<0.001$) and free beta-HCG ($p=0.029$) values of pregnant women with HG were higher than controls. In the HG group, the placental thickness was positively and weakly correlated with gestational week ($p<0.001$) and CRL ($p<0.001$). We also found that higher CRL values and the presence of HG were related to increased placental thickness ($R^2=0.159$, $p<0.001$) by performing linear regression analysis.

Conclusion: Being diagnosed with HG and having increased CRL is related to increased placental thickness. In relation to this result, increased placental thickness and free beta-HCG also seem to cause a higher risk for HG.

INTRODUCTION

Up to 80% of all pregnant women experience some degree of nausea and vomiting of pregnancy (NVP).[1] Nausea and vomiting during pregnancy begins approximately at 6–8 weeks of gestation and decreases around 16–20 weeks.[2] Hyperemesis gravidarum (HG) is persistent nausea and vomiting during pregnancy and is seen in approximately 0.3–2.0% of all pregnancies.[3]

According to the American College of Obstetricians and Gynecologists (ACOG) guidelines on nausea and vomiting (2018), there is still no worldwide accepted definition for HG. The most frequently accepted criteria for the diagnosis of HG are permanent vomiting, an acute sign of hunger (usually ketonuria), electrolyte abnormalities, acid–base disorders, and weight loss.[4] HG can also occur with signs and symptoms of severe dehydration, such as orthostatic hypotension, tachycardia, dry skin, mood changes, and lethargy.[5] The most common reason for hospital admission in the first half of pregnancy is HG.[2,6] Apart from hospitalization, HG causes additional doctor visits and emergency visits during pregnancy.[7]

The pathophysiology of HG remains an active area of research. No single mechanism has been identified as the sole cause of HG. Although various etiologies are being explored, a combination of these factors is likely to be responsible for the onset of the disease.[7] Multiple pregnancy, molar pregnancy, maternal age, genetic predisposi-

tion, parity, ethnicity, marital status, smoking, alcohol use, unexpected pregnancies, depression or psychiatric illness, lower socioeconomic level, history of hyperemesis, diabetes, low body mass index (BMI), asthma, hyperthyroidism, female fetus, dysmenorrhea, urinary tract infections, peptic ulceration, and other gastrointestinal disorders are among the factors that are associated with the development of HG.[3,8,9]

The placenta is a unique gestational body that is responsible for the majority of essential pregnancy functions, including fetal support, nutrition, and protection. One of the most important functions of the human placenta is the placental endocrine function, that is, the capacity to synthesize important hormones and other mediators that are crucial for pregnancy success.[10] The combined test that evaluates pregnancy-associated plasma protein-A (PAPP-A), free beta-human chorionic gonadotropin (beta-HCG), and nuchal translucency is widely used in Trisomy 21 screening.[11,12] Serum beta-HCG concentrations and NVP symptoms peak simultaneously in early pregnancy. Also, increased levels of beta-HCG can affect the regions of the brain that affect nausea, directly or indirectly. Therefore, some have suggested that beta-HCG plays a role in the development of NVP and HG.[7]

As placenta is the first organ to show disease-related changes during pregnancy, placental features may play a role in screening pregnancy complications.[13] After performing a detailed literature review, we found no studies evaluating the possible relationship between placental thickness and HG.

The aim of this study was to evaluate whether HG was associated with placental thickness and PAPP-A and beta-HCG levels.

MATERIALS AND METHODS

This case–control study was performed between June 2019 and December 2019. Ethics committee approval for this case–control study was obtained prior to conducting the study (reference number: 2019/514/154/19). The research was carried out with pregnant women who attended follow-up investigations in the gynecology and obstetrics outpatient. The rights of all participants were protected, and written informed consent was obtained before the procedures according to the Helsinki Declaration.

At the time of the study, 265 pregnant women applied to the clinic between 11 and 14 weeks of gestation to have a first trimester screening test (combined test). Among these pregnant women, 93 with a history of hospitalization one or more times with the diagnosis of HG in their current pregnancy constituted the HG group and 172 pregnant women without any health problems constituted the control group. HG was diagnosed according to ACOG criteria.[4] Having a diagnosis of multiple pregnancy, fetal anomaly, any systemic disease (diseases of the gastrointestinal system, thyroid, diabetes, etc.), those with eccentric umbilical cord, women older than 45 and younger than 18 years of age at the time of pregnancy, and those with a crown-rump length (CRL) value of <45 or >85 mm were excluded from the study. Written informed consent was obtained from the patients who agreed to participate in the study after giving detailed information about the purpose and scope of the study to the pregnant women who applied to the clinic for routine combined testing.

Anthropometric, demographic, and obstetric characteristics, including age, weight (kg), height (cm), BMI (kg/m^2), gravida, parity, miscarriage, smoking, gestational week, were recorded. Transabdominal ultrasonography (USG) of all patients was performed by the same experienced gynecologist and obstetrician. A Voluson E6 (GE, USA)-type device was used in all cases, and measurements were made with a 3.5–5 MHz ultrasound probe. Nuchal translucency, CRL (mm), and placental thickness measurements were done using USG. Also, uterine artery Doppler investigations were performed on both uterine sides to measure and calculate mean uterine artery pulsatility index (PI) and resistivity index (RI) according to the International Society of Ultrasound in Obstetrics and Gynecology criteria.[14] Placental thickness was measured in millimeters (mm) from the cord insertion site. At least three measurements were made, and their averages were taken as the final result in each patient. After the measurement of the CRL, the result of each case was assessed for compatibility with the last menstruation period. If the mismatch between the last menstrual period and USG was more than 5 days, the week of gestation determined via USG was considered correct. Blood tests of the patients were performed to complete the combined test. IMMULITE 2000 Siemens, which operates chemiluminescence principles using the original reagents, was used for reading PAPP-A and free beta-HCG biomarkers, and PRISCA 5 SOFTWARE was used for processing the data and the risk of trisomy 21. PAPP-A and free beta-HCG MoM values were recorded from the laboratory reports.

Statistical analysis

All analyses were performed on SPSS v21 (SPSS, Inc., Chicago, IL, USA). Q–Q and histogram plots were used to determine whether variables were normally distributed. The data were given as mean ± standard deviation (SD) or median (minimum–maximum) for continuous variables with regard to the normality of distribution and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed using the independent samples t-test. Non-normally distributed variables were analyzed using the Mann–Whitney U test. Pearson or Spearman's correlation coefficients were calculated to assess the relationship between continuous variables. Logistic regression analysis (forward conditional method) was performed to determine the risk factors for HG. Multiple linear regression analysis (stepwise selection method) was performed to determine factors related to placental thickness. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

The average age of pregnant women in the study group was 29.54±4.94 (min–max: 18–42) years. Placental thickness (p<0.001) and free beta-HCG (p=0.029) of pregnant women diagnosed with HG were significantly higher than the values of the control group. Groups were similar in terms of age, weight, height, BMI, gravida, parity, miscarriage, smoking, gestational week, CRL, PI, RI, PAPP-A, and nuchal translucency (Table 1).

We performed logistic regression analysis to determine significant risk factors for HG. We found higher placental thickness (p<0.001) and higher free beta-HCG (p=0.003) (Table 2) were related to increased risk for HG. The other variables included in the model, such as age (p=0.229), gestational week (p=0.853), CRL (p=0.354), PI (p=0.922), RI (p=0.435), PAPP-A (p=0.850), and nuchal translucency (p=0.606), were nonsignificant with logistic regression analysis.

In the whole study group, the placental thickness was found to have weak positive correlations with gestational week (r=0.272, p<0.001) and CRL (r=0.312, p<0.001). In the control group, very weak positive correlations were found between placental thickness and gestational week (r=0.174, p=0.023) and CRL (r=0.226, p=0.003). When patients with HG were analyzed, we found that the placental thickness was positively and weakly correlated with gestational week (r=0.455, p<0.001) and CRL (r=0.476, p<0.001) (Table 3).

We performed linear regression analysis to determine the significant factors related to placental thickness. We found that higher CRL values and the presence of HG were related to increased placental thickness (p<0.001, R^2=0.159). Other parameters included in the model showed no independent relationship with placental thickness, including age (p=0.573), week (p=0.394), PI (p=0.138), RI (p=0.173), PAPP-A (p=0.667), free beta-HCG (p=0.714), and nuchal translucency (p=0.288).

Table 1. Summary of patients' characteristics with regard to groups

	Groups		Total	p
	Control group (n=172)	HG group (n=93)		
Age in years	29.88±4.81	28.89±5.15	29.54±4.94	0.119
Weight (kg)	64.09±10.83	64.16±11.10	64.11±10.90	0.958
Height (cm)	161.79±6.13	162.18±5.71	161.93±5.98	0.611
BMI (kg/m^2)	24.48±3.91	24.39±3.98	24.45±3.93	0.860
Gravida	2 (1–8)	2 (1–5)	2 (1–8)	0.749
Parity	1 (0–3)	1 (0–4)	1 (0–4)	0.407
Miscarriage	0 (0–6)	0 (0–3)	0 (0–6)	0.711
Smoking	32 (18.60%)	14 (15.05%)	46 (17.36%)	0.577
Gestational week	13 (11–14)	13 (11–14)	13 (11–14)	0.165
CRL (mm)	63.38±9.46	63.90±9.11	63.57±9.32	0.669
Placental Thickness (mm)	17.21±3.12	18.99±3.44	17.83±3.34	<0.001
Uterine artery PI	1.87±0.59	1.83±0.64	1.86±0.61	0.679
Uterine artery RI	0.76±0.11	0.76±0.13	0.76±0.12	0.853
PAPP-A (MoM)	1.16 (0.32–3.43)	1.11 (0.24–5.19)	1.16 (0.24–5.19)	0.743
≤0.8	46 (26.74%)	28 (30.11%)	74 (27.92%)	0.560
>0.8	126 (73.26%)	65 (69.89%)	191 (72.08%)	
Free beta-HCG (MoM)	1.03 (0.31–2.54)	1.13 (0.16–2.94)	1.05 (0.16–2.94)	0.029
NT (mm)	0.77 (0.36–1.98)	0.74 (0.48–2.12)	0.76 (0.36–2.12)	0.307

Data are given as mean±standard deviation or median (minimum - maximum) for continuous variables with regard to normality of distribution and as frequency (percentage) for categorical variables. BMI: Body mass index; CRL: Crown-rump length; PI: Pulsatility index; RI: Resistivity index; PAPP-A: Pregnancy-associated plasma protein-A; MoM: Free beta-HCG values; HCG: Human chorionic gonadotropin; NT: Nuchal translucency.

Table 2. Significant risk factors for the hyperemesis gravidarum, multiple logistic regression analysis

	Unstandardized β	Standard Error	Wald	p	Exp (β)	95.0% Confidence Interval for β	
(Constant)	-4.603	0.863	28.424	<0.001			
Placental Thickness(mm)	0.168	0.042	16.064	<0.001	1.183	1.090	1.285
Free beta-HCG (MoM)	0.816	0.279	8.558	0.003	2.262	1.309	3.908

Dependent Variable: Groups (HG group); Nagelkerke R^2=0.131. HCG: Human chorionic gonadotropin; MoM: Free beta-HCG values.

Table 3. Relationship between variables

	Placental thickness (mm)	Gestational week	CRL (mm)	PAPP-A (MoM)	Free beta-HCG (MoM)
Total (n=265)					
Placental thickness (mm)	1	0.272**	0.312**	0.083	-0.005
Gestational week	<0.001	1	0.910**	0.199**	-0.006
CRL (mm)	<0.001	<0.001	1	0.162**	-0.027
PAPP-A (MoM)	0.180	0.001	0.008	1	0.260**
Free beta-HCG (MoM)	0.939	0.928	0.659	<0.001	1
Control group (n=172)					
Placental thickness (mm)	1	0.174*	0.226**	0.055	-0.044
Gestational week	0.023	1	0.918**	0.187*	-0.029
CRL (mm)	0.003	<0.001	1	0.145	-0.034
PAPP-A (MoM)	0.472	0.014	0.059	1	0.266**
Free beta-HCG (MoM)	0.567	0.702	0.661	<0.001	1
HG group (n=93)					
Placental thickness (mm)	1	0.455**	0.476**	0.162	-0.030
Gestational week	<0.001	1	0.907**	0.225*	0.025
CRL (mm)	<0.001	<0.001	1	0.194	-0.016
PAPP-A (MoM)	0.121	0.030	0.062	1	0.261*
Free beta-HCG (MoM)	0.778	0.815	0.876	0.011	1

Upper triangles represent correlation coefficients while lower triangles represent p-values. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). CRL: Crown-rump length; PAPP-A: Pregnancy-associated plasma protein-A; MoM: Free beta-HCG values; HCG: Human chorionic gonadotropin.

DISCUSSION

The etiology of HG, which is associated with significant morbidity, mortality, and high treatment costs in pregnancies, has not been fully understood. It is probably of multifactorial origin.[15,16] In this study, we evaluated the relationship between HG and parameters such as placental thickness, PAPP-A, and beta-HCG values. Beta-HCG and PAPP-A are placental hormones, and as mentioned earlier, beta-HCG plays a role in the pathophysiology of HG. We thought that placental thickness may play a role in the placental hormone levels and increased hormone levels, especially beta-HCG levels may cause HG. Therefore, we wanted to analyze placental thickness, PAPP-A, beta-HCG values, and HG relationship based on this this belief.

As the placenta is closely related to the fetus and mother, it often reflects the condition of both the mother and the fetus.[17] The most accurate estimate of placental size can be determined with placental volume. However, while placental volume measurement is very complex and difficult for routine use, measurement of placental thickness is relatively simple and clinically useful. Placental thickness outside the normal limits is well known as a diagnostic precursor of a wide range of pathological events.[18] Mesdaghi-Nia et al.[19] reported that a decrease in PAPP-A level increased the risk of placental thickness. Another study reported that there was a positive correlation between PAPP-A and beta-HCG levels and placental thickness between the 5th and 8th week of gestation; interestingly, this correlation was absent after the 8th gestational week.[20] Uysal et al.[21] found no relationship between placental thickness and PAPP-A levels. In our study, no significant relationship was detected between placental thickness and beta-HCG and PAPP-A levels. In addition, Vachon-Marceau et al.[22] reported a positive correlation between placental thickness and CRL, and many other previous studies have reported a correlation between placental thickness and gestational week.[17,23–25] We also revealed a positive correlation between the gestational week and placental thickness and demonstrated a link between CRL and the thickness of the placenta.

In the literature, an increase in the placental thickness can be seen in many pathological conditions such as gestational diabetes, intrauterine infections, and hydrops fetalis.[26] To our knowledge, this is the first study demonstrating the relationsip between HG status and placental thickness, PAPP-A, and beta-HCG levels. Our multiple regression model revealed that both CRL and the presence of HG were independently influential on placental thickness. The simple but important fact that HG presence emerged as an independent factor on placental thickness (along with CRL) is quite remarkable. However, as there are many other events related to placental thickness and the predictive power of our regression analysis is low (R^2=0.159), just an increase in placental thickness is not enough for the diagnosis of HG. However, it may be thought that increased placental thickness in pregnant women suspected of having HG may support the diagnosis.

Although the relationship of placental thickness and HG requires confirmation from further studies, and accepting the fact that measurement of placental thickness is not absolutely objective, we believe our results may indicate an under-researched area. Thus, in future studies, the underlying mechanisms involved in the relationship between HG and placental thickness should be determined, given the fact that these results are supported by future results. Also, it seems to us that the side-by-side evaluation of factors associated with placental thickness and HG risk factors could yield important results, especially in large, community-based multicenter studies.

The PAPP-A is a metalloproteinase secreted from the placenta during pregnancy, and it is known to be instrumental for successful implantation.[20] PAPP-A facilitates the actions of the insulin-like growth factor family to promote placental growth and function.[19] Low PAPP-A levels in the first trimester are reported to be strongly associated with a number of adverse pregnancy outcomes, such as preeclampsia, intrauterine growth retardation, and stillbirth.[27,28] In this study, we found that there was no difference between the groups in terms of PAPP-A levels, indicating that it did not contribute to HG development.[29] Contrastingly, in a study by Derbent et al.[30] that included 115 HG patients, PAPP-A was reported to be a risk factor for HG. Even though we did find that a higher percentage of patients with HG had PAPP-A values lower than 0.8, there were no significant differences between groups even when categorical comparisons were performed according to this cutoff value.

In pregnancy, the prevalence of HG symptoms is at the highest level when beta-HCG reaches its peak level. Therefore, a high concentration of beta-HCG has been proposed as one of the causes of HG.[31] It is among the possible mechanisms of action of beta-HCG, especially considering that it stimulates secretory processes in the upper gastrointestinal tract. Furthermore, its nonspecific stimulation of the thyroid stimulating hormone receptor may be another mechanism by which it contributes to the development of HG.[32] In the current study, we found that the beta-HCG value of pregnant women with HG to be significantly higher than that of pregnant women in the control group. In logistic regression analysis, we found that the increase in beta-HCG level was associated with an increased risk of HG. Similarly, in some studies, beta-HCG has been reported to be significantly higher in the HG group than in the control group.[30,33,34] However, there are also a considerable number of studies reporting that there is no difference in terms of beta-HCG levels between pregnant women diagnosed with HG and healthy pregnant women.[29,31,35,36] Despite the lack of universally accepted results on this topic, it is compelling to suggest that beta-HCG levels may in fact be related to the development of HG due to our significant results with multiple regression analysis.

One of the limitations of our research is that the long-term outcomes of pregnant women, including later stages of pregnancy, have not been evaluated. Therefore, the evidence level of the research is lower than cohort studies. Another limitation is that the number of cases examined in the research is low, and these patients were gathered from a single center. However, it is one of the few studies that have evaluated a large spectrum of possible risk factors for HG in a case–control design.

The present study indicated that beta-HCG seems to be an important parameter supporting the diagnosis of HG. We believe that it should only be considered in the presence of clinical and laboratory findings suspicious for HG. In addition, PAPP-A was not associated with either placental thickness or HG diagnosis. The most striking finding of our research was that increased placental thickness was associated with the risk of HG. More detailed research is needed to elucidate the relationship between HG and placental thickness.

Ethics Committee Approval

This study approved by the Kartal Dr. Lutfi Kirdar Training and Research Hospital Clinical Research Ethics Committee (Date: 29.05.2019, Decision No: 2019/514/154/19).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: G.Y., P.Y., E.M.; Design: G.Y., P.Y., E.M., D.K.; Supervision: G.Y., A.K.; Materials: G.Y., E.C.G., G.B., E.M.; Data: G.Y., G.B., E.C.G.; Analysis: B.K., K.T., A.K., G.B.; Literature search: B.K., K.T., D.K., E.C.G.; Writing: G.Y., P.Y., D.K.; Critical revision: G.Y., A.K., K.T., B.K.

Conflict of Interest

None declared.

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Hiperemezis Gravidarum ve Plasenta Kalınlığı, PAPP-A ve Serbest Beta-HCG ile İlişkisi: Olgu Kontrol Çalışması

Amaç: Çalışmanın amacı, hiperemezis gravidarum ile plasenta kalınlığı, gebelikle ilişkili plazma protein-A ve serbest beta-insan koryonik gonadotropin düzeyleri arasındaki ilişkileri değerlendirmektir.

Gereç ve Yöntem: Bu çalışmaya 11–14. gebelik haftaları arasında kadın hastalıkları ve doğum polikliniğine kombine test için başvuran toplam 263 gebe (93 HG'li ve 172 kontrol) dahil edildi. Baş-popo mesafesi (mm) ultrasonografi ile ölçüldü ve gebelikle ilişkili plazma protein-A ve serbest beta-insan koryonik gonadotropin değerleri (MoM) laboratuvar sonuçlarından kaydedildi.

Bulgular: Hiperemezis gravidarumlu gebelerin plasenta kalınlığı ($p<0.001$) ve serbest beta-insan koryonik gonadotropin ($p=0.029$) değerleri kontrol grubuna göre daha yüksekti. Hiperemezis gravidarum grubunda plasenta kalınlığı, gebelik haftası ($p<0.001$) ve baş-popo uzunluğu ($p<0.001$) ile pozitif ve zayıf korelasyon gösterdi. Lineer regresyon analizinde daha yüksek baş-popo mesafesi değerleri ve hiperemezis gravidarum varlığının artmış plasenta kalınlığı ($R^2=0.159$, $p<0.001$) ile ilişkili olduğu saptandı.

Sonuç: Hiperemezis gravidarum tanısı konması ve baş-popo mesafesinin artması, artmış plasenta kalınlığı ile ilişkilidir. Bu sonuçla bağlantılı olarak, artmış plasental kalınlık ve serbest beta insan koryonik gonadotropinin de hiperemezis gravidarum için daha yüksek riske neden olduğu görülmektedir.

Anahtar Sözcükler: Gebelikle ilişkili plazma protein-a; hiperemezis gravidarum; koryonik gonadotropin; plasenta, plasental kalınlık.