Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Serum Zinc Concentration and Helicobacter Pylori Serology in Hyperemesis Gravidarum

Evrim ERDEMOĞLU, Mehmet GÜNEY, Tuğçe ÇİMEN, Tamer MUNGAN

Isparta, Turkey

OBJECTIVE: Plasma zinc levels and possible relationship with Helicobacter Pylori (HP) serology positivity in women with hyperemesis gravidarum (HEG) are studied in order to test hypothesis decreased zinc levels possibly induced by HP might have a pathogenic role in HEG.

STUDY DESIGN: Thirty pregnant women with HEG and controls were enrolled into study. Zinc concentrations were determined by atomic absorption spectrophotometry. Specific serum antibodies directed against HP were measured.

RESULTS: HP IgG antibodies were detected in 76.6% of HEG women and in 43.3% of controls ($p<0.05$). Mean of zinc level was 96.9±40.1 micromol/l and 80.9±16.6 micromol/l in HEG and controls, respectively ($p>0.05$). Zinc levels were not correlated either with helicobacter pylori serology or study groups ($p>0.05$).

CONCLUSION: Serum zinc level is not altered by HEG and HP infection. There might be a possible association between HEG and HP, however there was no relation between HEG, HP and zinc.

Key Words: Hyperemesis gravidarum, Zinc, Helicobacter pylori, Serology

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Introduction

Nausea and vomiting is associated with 70 to 80% of pregnancies.[1] Hyperemesis gravidarum (HEG) is a severe form of these disorders with persistent nausea and frequent vomiting. HEG is reported to occur in 0.5 to 1% of all pregnancies.[2] The pathophysiology of HEG is poorly understood and its etiology is unknown. It has been reported that higher HCG levels, higher estradiol levels, abnormal progesterone levels, hepatic dysfunction, thyroid dysfunction, parathyroid dysfunction, nutritional deficiencies cause HEG.[3,4] Recently, Helicobacter Pylori (HP) has been suggested as a possible etiological factor.[5,6]

Zinc participates in protein and carbonhydrate metabolism, nucleic acid synthesis, cellular division and differentiation.[7] Zinc deficient experimental animals may have features similar to HEG, such as anorexia, dietary craving and aversion.[8] Therefore, zinc deficiency was proposed to be an etiological agent for HEG. However, plasma zinc levels are reported to be elevated, decreased or not altered in patients with HEG.[8,9]

HP critically needs zinc for growth [10] and may also impair absorption of nutrients.[11] HP may be related to zinc deficiency in pregnancy and HEG. To our knowledge (Pubmed search; 1966-2008; English language; search terms: hyperemesis gravidarum; helicobacter pylori; zinc) the relation between HP and zinc has not been studied in HEG women. We hypothesized that decreased zinc levels possibly induced by HP might have a pathogenic role in HEG. We therefore evaluated plasma zinc levels and its possible relationship with HP serology positivity in women with HEG.

Material and Method

Sixty pregnant women were enrolled into the study from the department of Obstetrics and Gynecology, Süleyman Demirel University Medical School (Isparta, Turkey) during 2007 and 2008. All women were provided informed consent and the study was approved by Institutional Review Board. Sample size was both calculated for comparing means with a 20% difference in mean of plasma zinc level in HP positive women and HP negative women. Assuming the background rate of 50% in our centre,[5] twenty-six with HEG and twenty-six healthy pregnant women were enough to include into the study for 80% power at alpha 0.05. All subjects were between 7-12 gestational weeks and groups were matched for gravida. Gestational age was calculated using last menstrual period and

Department of Obstetrics and Gynecology Faculty of Medicine Süleyman Demirel University, Isparta

Address of Correspondence: *Evrim Erdemoğlu*
Süleyman Demirel Üniversitesi
Tıp Fakültesi Kadın Hastalıkları ve
Doğum Ana Bilim Dalı
Isparta

evrimmd@yahoo.com
erdemoglu@med.sdu.edu.tr

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crown-rump length measurement in ultrasonography. Women with different gestational age according to last menstrual period and ultrasonographic measurements were excluded from the study.

Inclusion criteria for the diagnosis of HEG were vomiting more than four times a day, ketonuria and weight loss of at least 5%. Women with thyroid disease, multiple pregnancy, hepatitis, trophoblastic disease, inflammatory disease, gastroenteritis, history of recent use of any antibiotics or any medication (including vitamin supplementation) and history of peptic ulcer treatment were excluded from the study. All patients were admitted to receive inpatient treatment for hyperemesis. Biochemical tests to measure blood sugar, electrolytes, renal and hepatic functions and hormonal tests including Thyroid-stimulating hormone (TSH), free thyroxine (FT3) and free tri-iodothyronine (FT3) were conducted on admission. Venous blood samples were taken and collected separately in polypropylene tubes before admission. Each blood sample was centrifuged at 3000 rpm for 15 minutes, and the separated serum was stored at -80°C until analysis.

Zinc concentrations were determined by atomic absorption spectrophotometry. Stocked solutions of 1 ml of zinc (1mg/ml) was diluted to 100 ml with deionised water for preparation of standard solution. Calibration standard was prepared as 0.1, 0.2 and 0.3 ppm. Plasma samples were diluted in the ratio of 5:1 and the concentrations were calculated from the absorption values read on the atomic absorption spectrophotometer.

Specific serum antibodies directed against HP were measured by enzyme linked immunosorbent assay (HP ELISA IgG, Virotech, Genzyme, GmbH, Germany). An IgG index of >11 Arbitrary units (Au)/ml was considered positive and <9 Au/ml was regarded as negative. IgG levels between 9 and 11 Au/ml were regarded as indeterminate and required a repeat test in 2 to 4 weeks.

Statistical Analyses

Demographical data and zinc levels were expressed as mean ± standard deviation. HP IgG serology was expressed on a binary scale as positive or negative. Statistical analysis was conducted using Student t test, binary logistic regression, Mann-Whitney U, as appropriate. Analyses were performed by with SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and statistical significant level was set to 0.05.

Results

A total of 30 control and 30 women with HEG were enrolled to the study. There were no statistically significant differences between the groups with regard to age, gravidity, parity, body mass index and gestational age (Table 1). HP IgG antibodies were detected in 23 out of 30 (76.6%) of women with HEG and in 13 out of 30 (43.3%) of controls (p<0.05). Mean of zinc level was 96.9±40.1 micromol/l in the HEG women. Mean of zinc level in the control group was 80.9±16.6 micromol/l (p>0.05). Zinc levels were not correlated either with helicobacter pylori serology or study groups (p>0.05). However, HP serology was significantly related with HEG (OR:2,8, 95%CI:1,2-16.9, p<0.05).

Table 1: Demographic characteristics, helicobacter pylori (HP) seropositivity rate and serum zinc levels in study groups.

	Hyperemesis Gravidarum n=30	Controls n=30	p
Age	27.3±4.6	27.2±3.4	>0.05
Gravida	1.8±0.9	1.9±0.9	>0.05
Parity	0.5±0.5	0.7±0.8	>0.05
Gestational Age (weeks)	9.8±1.6	10.3±1.3	>0.05
BMI (Kg/m²)	21.4±2.1	22.8±2.6	>0.05
HP IgG seropositivity	23/30 (76.6%)	13/30 (43.3%)	<0.05
Serum Zinc Value (micromol/l)	96.9±40.1	80.9±16.6	>0.05

Discussion

In the present study, rate of HP IgG serospositivity was significantly higher in women with HEG than in control subjects. Kocak et. al reported that 92% of HEG women were seropositive for HP as compared to 45% of controls, in accordance with our results.[12] Karadeniz et. al. reported that 67% of women with HEG and 79% of control were seropositive for HP IgG (p>0.05). In this study, HP stool antigen positivity was also similar between the HEG and control group.[13] Goldberg et. al reviewed the studies published in 1996-2007 examining the relationship between HEG and HP serology. They concluded that there is an association between HEG and HP.[14]

The limitation of the present study was using serology for testing. Endoscopic gastric biopsy is claimed to be the gold standard for diagnosis of active HP infection.[15] However, endoscopy is not desired in pregnancy.[5,14,16,17] Serologic HP IgG detection might possibly replace biopsy in certain situations such as pregnancy.[14,16] Measurement of serum IgA and IgM is another method of detecting active HP infection.[17] IgA and IgM are found in a few patients with HP infection.[14,18] It is reported that sensitivity and specifity of serum IgG is higher than serum IgA and/or IgM.[14,19] Stool antigen test might be a good alternative for detection of HP in pregnancy, but there is no consensus regarding the threshold value.[17,20] Therefore, we preferred serum IgG for diagnosis of HP. Although serum results cannot distinguish between past or active infection, the fact that most patients were quite young and from areas with

high H pylori prevalence suggests that there is a good chance they had active infections.[14] This suggests that despite limitations in testing, the serological tests are fairly reliable in the selected populations.[14]

The hypothesis that decreased zinc levels possibly induced by HP might have a pathogenic role in was rejected; as our findings showed that zinc levels were not different between women with HEG and control subjects. Besides, there was no relationship between HP IgG seropositivity and serum zinc values. Lao et. al reported that zinc levels are not altered in women with HEG.[8] Although zinc levels could be in normal range due to dehydration. Dökmeci et. al. reported hyperemetic women had normal tissue zinc, copper and magnesium concentrations, and higher zinc and copper levels which was normalized after hydration treatment.[21] These and our findings support that there is probably no association between HEG, HP and zinc levels.

In conclusion, we suggest that there might be a possible association between HP and HEG, although no relationship between HEG, HP and serum zinc level was found. Therefore, zinc does not seem to be a possible cause of HEG. Besides zinc level was not altered by HP infection and supplementation of zinc should not be considered in HEG with HP infection. Additional studies are needed to support our results and to clarify the possible relationship of zinc and HP in HEG.

Hiperemesis Gravidarum'da Serum Çinko Konsantrasyonu ve Helikobakter Pilori Serolojisi

AMAÇ: Hiperemezis gravidarumlu (HEG) Helikobakter pilori (HP) serolojisi pozitif hastalar ile HP'nin neden olduğu ve HEG hastalarında patogenezde rolü olabilecek düşük plazma çinko seviyesi arasındaki olası ilişkinin anlaşılmasıdır.

GEREÇ VE YÖNTEM: 30 HEG hastası ve kontroller çalışmaya dahil edilmiştir. Plazma çinko seviyeleri atomik absorbsiyon spektrofotometri ile ölçülmüş ve HP antikor seviyeleri değerlendirilmiştir.

BULGULAR: HP IG antikorları HEG hastalarında %76.6 oranında, kontrollerde ise %43.3 oranında saptanmıştır (p<00.5). HEG hastalarında ortalama çinko seviyeleri 96.9±40.1 micromol/l kontrol grubunda ise 80.9±16.6 micromol/l seviyelerinde saptanmıştır. Serum çinko seviyeleri HP seroloji pozitifliği ve kontrol grubu arasında anlamlı farklılık saptanmamıştır.

SONUÇ: Serum çinko seviyeleri HEG ve HP enfeksiyonu ile ilişkili bulunmamıştır. HEG ve HP arasında olası ilişki bulunabilir ancak HEG, HP ve çinko seviyeleri arasında ilişki saptanmamıştır.

Anahtar Kelimeler: Hiperemesis gravidarum, Çinko, Helikobakter pylori, Seroloji

References

1. Lacroix R, Easton E, Melack R. Nausea and vomiting during pregnancy A prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol 2000; 182:931-7.
2. Broussard CN, Richter JE. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am 1998; 27:123–51.
3. Verberg MF, Gillott DJ, Al-Fardan N et al. Hyperemesis gravidarum, a literature review. Hum Reprod Update 2005; 11:527-39.
4. Lagiou P, Tamimi R, Mucci LA et al. Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone: a prospective study. Obstet Gynecol 2003; 101:634-9.
5. Güney M, Oral B, Mungan T. Serum lipid peroxidation and antioxidant potential levels in hyperemesis gravidarum. Am J Perinatol 2007; 24:283-9.
6. Jacoby EB, Porter KB. Helicobacter pylori infection and persistent hyperemesis gravidarum. Am J Perinatol 1999; 16:85-8.
7. Izquierdo Alvarez S, Castañón SG, Ruata ML, et al. Updating of normal levels of copper, zinc and selenium in serum of pregnant women. J Trace Elem Med Biol 2007; 21:4952.
8. Lao TT, Chin RK, Mak YT, Panesar NS. Plasma zinc concentration and thyroid function in hyperemetic pregnancies. Acta Obstet Gynecol Scand 1988; 67:599-604.
9. Tekşen F, Dökmeci F, Kavas G, Aribal Kocatürk P, Cengiz L. Copper, zinc and magnesium status in hyperemesis gravidarum. J Obstet Gynaecol 2001; 21:46-8.
10. Testerman TL, Conn PB, Mobley HL, McGee DJ. Nutritional requirements and antibiotic resistance patterns of Helicobacter species in chemically defined media. J Clin Microbiol 2006; 44:1650-8.
11. Akcam M, Ozdem S, Yilmaz A, Gultekin M, Artan R. Serum ferritin, vitamin B (12), folate, and zinc levels in children infected with Helicobacter pylori. Dig Dis Sci 2007;52:405.
12. Koçak I, Akcan Y, Üstün C, Demirel C, Cengiz L, Yanik FF. Helicobacter pylori seropositivity in patients with hyperemesis gravidarum. Int J Gynaecol Obstet 1999; 66: 251-4.
13. Karadeniy RS, Ozdegirmenci O, Altay MM, et al. Helicobacter pylori seropositivity and stool antigen in patients with hyperemesis gravidarum. Infect Dis Obstet Gynecol 2006; 2006:73073.
14 Goldberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol 2007; 110:695-703.

15 Bagis T, Gumurdulu Y, Kayaselcuk F, Yilmaz ES, Killicadag E, Tarim E. Endoscopy in hyperemesis gravidarum and Helicobacter pylori infection. Int J Gynaecol Obstet 2002; 79:105-9.

16 Erdem A, Arslan M, Erdem M, Yildirim G, Himmetoglu O. Detection of Helicobacter pylori seropositivity in hyperemesis gravidarum and correlation with symptoms. Am J Perinatol 2002; 19:87–92.

17 Lee RH, Pan VL, Wing DA. The prevalence of Helicobacter pylori in the Hispanic population affected by hyperemesis gravidarum. Am J Obstet Gynecol 2005; 193:1024-7.

18 Rathbone BJ, Wyatt JI, Worsley BW, et al. Systemic and local antibody responses to gastric Campylobacter pyloridis in non-ulcer dyspepsia. Gut 1986; 27:642-7.

19 Laheij RJ, Straatman H, Jansen JB, Verbeek AL. Evaluation of commercially available Helicobacter pylori serology kits: a review. J Clin Microbiol 1998; 36:2803-9.

20 Syam A, Rani AA, Abdulla M, et al. Accuracy of Helicobacter pylori stool antigen for the detection of Helicobacter pylori infection in dyspeptic patients. World J Gastroenterol 2005; 11:386-8.

21 Sempértegui F, Díaz M, Mejía R, et al. Low concentrations of zinc in gastric mucosa are associated with increased severity of Helicobacter pylori-induced inflammation. Helicobacter. 2007; 12(1):43-8.