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Full Length Research Paper

Helicobacter pylori and CagAantibodies in hyperemesis gravidarum (HG)

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In order to determine whether infection with *Helicobacter pylori* and CagA strain is associated with hyperemesis gravidarum (HG), a study was conducted in Al- Zahra obstetrics and gynecology hospital in Tabriz, Iran between May 2007 and February 2008. Forty-four (44) pregnant women with the diagnosis of HG and forty-four (44) normal pregnant women of matched gestational age were included in this prospective study. Serum *H. pylori* immunoglobulin G antibody titer and CagAantibodies were measured for both groups of women. There was no difference in seropositivity of *H. pylori* antibody between subjects with hyperemesis when compared with controls. The prevalence of *H. pylori* infection with CagA + gene was significantly higher among control group when compared with study group. HG seems not to be associated with *H. pylori* infection. The results of this study suggested higher levels of CagA *H. pylori* infection in control groups.

Key words: *Helicobacter pylori*, hyperemesis gravidarum, CagA + gene.

INTRODUCTION

Warren and Marshall were the first people who described *Helicobacter pylori*. At first, they named the bacterium *Campylobacter pyloridis*. Later, it was named *Campylobacter pylori*. Since then, a large number of scientific articles have been published about *H pylori* and the research is ongoing to further clarify different aspects of *H. pylori* infection as it affects human health. The discovery of *H. pylori* in 1982 was the starting point of an immense change in the management of gastro duodenal diseases. At present, *H. pylori* is well recognized as the main pathogenic factor for chronic gastritis, peptic ulcer disease, and gastric cancer. *H. pylori* is a human pathogen, globally spread and the major cause of organic gastro duodenal diseases. The infection with the bacteria causes high morbidity and mortality (Selgrad et al., 2009; Malfertheiner and Selgrad, 2010; Malfertheiner et al., 2010) . The action of *H. pylori* is widely studied in literature and some studies now focus specifically on its association with nausea and vomiting (Notash et al., 2008; Penney, 2005). Nausea and vomiting during pregnancy begins between the fourth and seventh week after the last menstruation period in 80% of pregnant women and resolves by the 20th of gestation in all but 10% of these women (Quinla and Hill, 2003).

HG is a condition of intractable vomiting during pregnancy, leading to fluid, electrolyte and acid–base imbalance, nutritional deficiency and weight loss is often severe enough to require hospital admission. HG is a very common medical but poorly understood disorder and one for which many physicians have little sympathy. Possibly, this is due to the difficulty in understanding its pathogenesis and treating it (Abell and Riely, 1992). Based on available knowledge no single theory seems to provide an adequate explanation for HG. Prevalence of HG varies from 0.3 to 1.5% of all live births (Hod et al., 1994; Verberg et al., 2005). HG is the most common cause of hospitalization in the first half of pregnancy and is second only to preterm labor for pregnancy overall. HG can be associated with serious maternal and fetal morbidity such as Wernicke's encephalopathy, fetal growth restriction, and even maternal and fetal death (Verberg et al., 2005). A possible association between *H. pylori* infection and HG has been the focus of researching

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for some studies (Penney, 2005; Abell and Riely, 1992; Karadeniz et al., 2006). The Cytotoxin associated gene (CagA) is considered to be a marker for a genomic pathogenicity island and is being identified as a virulence factor for *H. pylori* (Kim et al., 2001). The aim of this study was to determine whether infection with *H. pylori* and CagA strain is associated with HG.

MATERIALS AND METHODS

A case-control study was conducted in Al- Zahra obstetrics and gynecology university hospital in Tabriz between 2007 and 2008. Forty-four pregnant women with the diagnosis of HG and forty-four normal pregnant women of matched gestational age were included in this prospective study (frequency matching). Controls were selected from the similar referrals to ensure common source population for the cases and controls. The criteria for HG were pernicious vomiting without any obvious cause except for pregnancy, weight loss of more than 3 kg or 5%, and the presence of at least one positive ketonuria (Jueckstock et al., 2010). Inclusion criteria for the study group included HG, age of 18- 39 years, gestation between 6 and 14 weeks and exclusion of other causes of vomiting such as hyperthyroidism, multiple gestation, gestational trophoblastic disease, psychological and gastrointestinal disorders (Karadeniz et al., 2006). The controls were matched by maternal and gestatonal age. Gestational age was determined by the last menstrual period and confirmed by real time ultrasonography. Serum *H. pylori* immunoglobulin G antibody titer was measured using enzyme-linked immunosorbent assay for both groups of women. The individual who performed the IgG test was blinded to the group assignment. 20 Au/ml (Arbitrary unit per milliliter) was considered positive and -15 Au/ml was regarded as negative. IgG levels between 15 and 20 Au/ml were regarded for 2 to 4 weeks (Kazerooni et al., 2002). The serum was further analyzed for the presence of antibodies to the CagA antigen using a commercial Western blot test (Brenner et al., 2004).

Statistical analysis

Data were analyzed using SPSS software, version 16.0 (SPSS, Chicago, IL, USA). The Pearson 2 test was used to assess possible association among categorical variables and the student t test was used for numerical variables. AP value less than 0.05 was considered as statistically significant. As the matching was not individual based, statistical tests usual for independant samples were used.

Ethical issues

Study was approved by the committee of ethics in Tabriz University of medical sciences. Informed consent was obtained from all patients examined.

RESULTS

A total of 44 subjects and 44 controls were enrolled in this study. Mean age of the participants in cases group was 25 to 26 years (range: 18 to 39 years) while mean years for control group was 26 to 28 years (range: 18 to 38 years). No statistical significant difference was found regarding maternal age and gestational age between cases and controls. *H. pylori* serum antibody test was positive in 36 out of 44 HG cases (81.8 %) and in the controls were 34 out of 44 (77.2%). The observed difference was not statistically different between the two groups. The odds ratio was calculated to be 1.3 with 95% confidence interval of 0.47 to 3.7. The odds ratio of CagA positive serology in HG was calculated to be 2.2 and the 95% confidence interval for it was 0.9 to 5.4. The mean (SD) of the IgG titers was not significantly different between the two groups, case group had 55.76 (30.12 Au/ml) compared to 48.19 (28.30 Au/ml) in the control group (Table 1).

No correlation was found between the IgG titer, gestational age, maternal age, and gravidity or parity.

DISCUSSION

Thus, the sero-prevalence rates of *H. pylori* infection in this study among pregnant women were high. It was not much different from the rate in other developing countries (Reshetnikov et al., 2003; Salih, 2009). It was also in accordance with a previous Iranian study (Kazerooni et al., 2002). The association between *H. pylori* transmission and the lower socio-economic status is well documented in literature (Ma et al., 1996; Karaca et al., 2004). Most our patients in a general hospital were from a low socio- economic status and that may explain the substantially higher prevalence of the infection. In addition, an association between pregnancy and susceptibility to *H. pylori* infection is also reported in literature (Quinla and Hill, 2003). Although not statistically significant, but our results showed an effect size tendency towards possible association of *H. pylori* infection and HG. Studies have sometimes found conflicting evidence of the role of *H. pylori* in severe nausea and vomiting during pregnancy and HG. However, this controversy just gets back to the effect size reported without adequate statistical significance measures. Lee et al. (2005) and Karadeniz et al. (2006) found a preventive tendency for *H. pylori* infection effect on HG, but in both cases the confidence interval of odds ratios included one, meaning lack of statistical significance of their findings (Lee et al., 2005; Karadeniz et al., 2006) . Similarly to our results, some studies have found the *H. pylori* to have higher descriptive proportions among patients with HG but without statistical signifi-cance (Berker et al., 2003; Cevrioglu et al., 2004; Jacobson et al., 2003). While some other studies have found an association between *H. pylori* infection and HG with significant statistical results (Kazerooni et al., 2002; Xia et al., 2004; Salimi-Khayati et al., 2003; KocakI et al., 1999; Hayakaw et al., 2000; Frigo et al., 1998; Erdem et al., 2002).

It has been suggested that the possession of the Cytotoxin- associated gene A (CagA), gene, are linked to increased pathogenicity of *H. pylori* strains. Briefly this study provides new data for further investigation into etiology and pathogenicity of $CagA^+$stain. Although, the

Table 1. Prevalence of *H. pilori* and CagA$^+$ gene infection in hyperemesis gravidarum and healthy controls.

Groups	n=44		P value
	Control group	Case group	
Infected with *H. pilori* (%)	34(77.2)	36(81.8)	0.6
Infected with CagA$^+$(%)	12(27.2)	20(45.4)	0.06
IgG titer : Mean (SD)	48.19(28.30)	55.76(30.12)	0.3

present study failed to find significant differences possibly due to lower study power regarding the main exposure variable, an interesting observation of the current study, was that 27.2% of case group women had CagA, whereas only 5.4% of control women had CagA. The results of this study suggest higher levels of CagA *H. pylori*-infection in control groups. Although only histological exams can be the best proof for the existence of *H. pylori* infection while we had used the serological method, but as can be referred to most of the literature addressing this research question, this may be acceptable considering the fact that ethical regulations are not usually compatible with conducting histological exams among pregnant women without HG. However, one solution can be the repeated serologic assessments before and through the pregnancy in cohort studies.

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