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Obstetrics and Gynecology

The Association Between Helicobacter Pylori Infection And Hyperemesis Gravidarum

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ABSTRACT

Background: Hyperemesis gravidarum (HG) is the severe kind of nausea and vomiting of gestation. The HG incidence is about 0.5-2.0%. For the diagnosis of HG there must be existence of 3 or more vomiting episodes throughout the day, weight losing of more than 5% and ketonuria. Studies have recently suggested that there is a correlation among emesis gravidarum and HG with Helicobacter pylori (H. pylori) infection. Serologically positive H. pylori infections were demonstrated in hyperemesis patients.
Aim of the study: The current work aimed to detect the correlation among H. pylori infections and HG throughout gestation.
Patients and Methods: The current work a case-control study carried out at the obstetric department of Al Zahra university hospitals in the interval from March 2021 till June 2021. It included 100 singleton pregnant women between 6-18 weeks of gestation that were referred from outpatient clinic.
Results: IgM anti-body titer was highly significant in cases compared to controls; also, IgM antibody titer in primigravida was highly significant in cases vs. controls. However, IgM antibody titer in multigravida was higher in cases in versus control group but without statistical significance difference. Moreover, IgM seropositivity was significantly more common in cases in comparison with controls.
Conclusion: study proposes that a correlation was existing among H. pylori infections and HG, permitting us to report that H. pylori must, consequently, taken into consideration as a risk-factor for HG.

Keywords: *Helicobacter Pylori, Hyperemesis gravidarum, pregnancy, multigravida.*

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INTRODUCTION

Nausea and vomiting throughout gestation, which is also recognized as 'morning sickness', affects between 70% and 80% of all pregnancies in the 1st trimester. Usually, it starts form 4- to 8-wks of pregnancy, however the signs might continue till the 16th–18th week. It is commonly a mild condition and self-limited. A little number of pregnancies have a more acute sequalae, with the severest shape recognized as hyperemesis gravidarum (HG) [1].

Almost 1 to 10 % of gestations, signs can stay till 20- to 22-wks [2].

HG is marked by permanent nausea and vomiting accompanied by ketosis and weight-losing (>5% of the weight before pregnancy). It may cause hypovolemia, electrolytes disturbance and acid-base imbalance, nutritional shortages, and even - in severe cases - death. Severe cases with hyperemesis require hospitalization in 0.3-2% of pregnancies [3].

Prevalence of HG varies between 0.3 and 1.5% of all live deliveries [3].

The exact etiology of HG isn't well known and is probably multifactorial in which psychological factors, disturbance of gastro-intestinal motility, hormonal changes, infections, immunological, metabolic and anatomical factors appear to intervene [4].

It is the commonest reason of hospital-stay in the 1st half of gestation and 2nd only afterward pre-term labour for gestation. It may be accompanying with serious maternal morbidities like Wernicke's encephalopathy and embryonic morbidity such as intrauterine growth retardation, and in severe cases maternal and fetal death may happen [1]

The H. pylori are considered as an important reason for gastritis in human beings and as an essential parameter in the pathogenesis of peptic ulcer. Many findings suggest that H. pylori are also included in the pathogenesis of tumour and lymphoma of the stomach [5].

In developing republics, 70- 90 % of the populations are diseased by the bacteria, while in industrialized countries the prevalence is smaller, ranging between 25% and 50% [1].

Many methods of H. pylori testing exist. Noninvasive examinations for H. pylori infections include the blood antibodies tests, the stool antigen testing, or with the carbon urea breathe testing (in which the case drinking urea labelled with ^{14}C or ^{13}C, then the bacteria absorbs the labelled urea creating labelled CO2 that could be measured in the patient breath). The other technique for H. pylori infections detection is endoscopic biopsy checking with a fast urease testing, histologic examinations, and microbic culture [6].

On other wise, serology specimens the whole abdominal where biopsy only specimens a little portion, and the inflammation process can be patchy, so serologic analyzing is considered to have higher sensitivity than diagnosis approaches including biopsy. The progress of H. pylori-specific fluorescent serum anti-body testing helps for easy and appropriate screening for H. pylori infections and because of its easy, economic and noninvasive test, it because probable to measure H. pylori infections in gravid females [1].

We aimed to detect the correlation among H. pylori infections and HG throughout gestation.

PATIENTS AND METHODS

This was a case-control investigation performed at the obstetric department of Al Zahra university hospitals in the interval from March 2021 till June 2021. It included 100 singleton pregnant women between 6-18 weeks of gestation that were referred from outpatient clinic.

They were divide into 2 groups: Group-A (studied group): This group included 50-females suffering from nausea and vomiting accompanying with losing of weight, ketonurea, electrolyte imbalance, elevated liver enzymes and alkalosis. Group B (control group): this group included 50 healthy pregnant women.

Exclusion criteria:

Women with clinical thyroid dysfunction or hyperthyroidism with pregnancy, women with medical disorders especially that cause vomiting as GIT disease with past history of peptic ulcer and those with multiple pregnancy or gestational trophoplastic disease.

All cases were exposed to the next: Complete history talking, general examinations, abdomen examination, trans-abdominal and Trans-vaginal pelvic sonogram, laboratory investigations by detection of h pylori igm by ELISA and all patients give written consent.

Principle of the assay

Enzyme Linked Immunoassay (ELISA):

It is an Enzyme Immuno-assay for qualitative and quantitative determinations of H. pylori Igm in the serum. The kits was supplied by BIOSEWOOM Co., Ltd#273-15, Wooyoung Techno center 1f, Sungsu 2-ga 3dong, Sungdong-gu,Seoul,Korea with sensitivity and specificity 98%.

Sampling and Specimen preparation: For each case, 5ml of blood were drawn by venipuncture and collected in sterile tubes. The blood samples were centrifuged for 15 minutes. Serum was collected and stored at 20 C until used.

Wells of the microtiter plates are coated with H. pylori antigens. When serum samples are added, anti HP IgM, if present, are caught via the antigens. The bound anti-HP IgM are noticed via adding antihuman IgM antibodies labeled with horseradish peroxidase, the enzymes caught on the solid shape acts on the substratum generating optical signals which is related to the quantity of anti-HP `IgM antibody existing in the specimen. IgM in the specimen can be determined using calibrated waves in units per milliliter (U/ml).

All samples and kits components were brought to room temperature (18-25 c) about 1 hour before use. - Liquid reagents were carefully mixed on vortex. - Preparation of the washing solution: The 20x concentrated solution was diluted to 1900ml of distilled water.

10 ML of each serum specimen was supplemented to 1ml of the specimen diluent. -100 ML of every diluted serum specimen prepared for standards usage were pipette to the suitable wells. -One well was left for the blank in which 100ML of the working substrate solution will be added. -The wells were covered with protective film and incubated for 60-min at 37^{o}. -Every well was then aspirated and washed 5-times 30-sec with the washing solutions via an automated microtitration plate washer. The excess of the washing solution was eliminated from the wells by inverting the plate for blotting and drying on a paper adsorbent pad. -100 ML of the enzyme conjugate solution has been supplemented to every well excluding the blank. -The wells were shielded with a protecting coating and incubated for 60-min at 37^{o}. -The washing step was repeated as previously mentioned. -100ML of the working substrate solution has been supplemented to all wells. -Wells were incubated for 20-min in dark at room temp. -100ML of the stopping solutions was supplemented to all wells. -The solution absorbance

in each well has been read via a microtitration plate reader set to double wavelengths measurements at 450-nm with back-ground wave-length correcting set at 620-nm. -A standardized curve was plotted with the identified concentration of the HP IgM standards on the X-oxis and the equivalent absorbances on the Y-axis. -The concentration of HP IgM in the samples were estimated by drawing the samples absorbances on the Y-axis, then plotting a horizontal line to meet the standardized curve. A vertical line was then drawn from this point to the X-axis denoting the IgM concentrations. This was done using a plate reader /PC interface.

Cut-off value: 20units/ml i.e. samples with HP IgM concentration higher than 20U/ml were considered positive for HP IgM and vice versa. i.e. samples with HP IgM concentration less than 13U/ml were considered negative for HP IgM and vice versa. Samples with HP IgM concentration between (13-20) U/ml were considered suspicious for IgM and to be repeated.

Statistical Analysis:

gathered data have been analyzed via IBM-SPSS 22.0 (SPSS Inc., Chicago, IL, USA). All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 counted as significant, p-value <0.001 was high significance and, P-value> 0.05 was Nonsignificant.

RESULTS

A nonsignificant change was found among the studied groups in regard to maternal ages, BMI, parity and GA at administration. (Table 1)

There was a nonsignificant change among the study groups in term of parity. (Table 2)

A significant change was found among the study groups in regard to hemoglobin and MCHC. (Table 3)

IgM antibody titer was highly significant in cases in comparison with control group; also, IgM antibody titer in primigravida was highly significant in patients in comparison with controls. However, IgM antibody titer in multigravida was higher in cases vs. controls but without statistical significance difference. Moreover, IgM seropositivity was significantly more common in cases vs. controls. (Table 4).

	Cases (n=50)	Control (n=50)	t	p
Age (years) Mean ± SD	26.68 ± 4.89	26.87 ± 4.91	0.194	0.847
BMI (kg/m2) Mean ± SD	25.6 ± 2.69	26.12 ± 2.84	0.939	0.349
GA (weeks) Mean ± SD	8.57 ± 2.14	8.93 ± 1.75	0.921	0.359

Table 1: Demographic characteristics and clinical data among the studied groups

	Cases (n=50)	Control (n=50)	$\chi 2$	P
Primigravida	22 (44%)	15 (30%)	2.1	0.149
Multiparous	28 (56%)	35 (70%)		

Table 2: Parity distribution among the studied groups.

	Cases (n=50)	Control (n=50)	t	P
Hemoglobin (g/dL) Mean ± SD	10.85 ± 1.19	11.27 ± 0.861	**2.02**	**0.046**
HCT (%) Mean± SD	31.29 ± 3.15	31.76 ± 2.25	.859	0.393
MCH (%) Mean± SD	27.24 ± 2.35	26.97 ± 2.38	.571	0.569
MCHC Mean± SD	29.73 ± 1.23	29.18 ± 1.11	**2.35**	**0.021**
PLT (x 10^3/L) Mean± SD	315.76 ± 46.81	311.26 ± 40.75	.513	0.609
TLC (x 10^3/L) Mean± SD	7.31 ± 2.73	7.15 ± 1.86	.342	0.733
ALT (U/L) Mean± SD	22.49 ± 7.34	21.36 ± 7.76	.748	0.456
AST (U/L)	20.37 ± 6.33	19.47 ± 6.51	.701	0.485

Mean± SD				
Creatinine (mg/dl) Median (Range)	0.74 (0.6 - 1)	0.8 (0.6 - 1.1)	z 1.32	0.127
Urea (mg/dL) Mean ± SD	17.25 ± 3.83	18.47 ± 3.64	1.63	0.106
RBS (mg/dl) Mean ± SD	137.75 ± 25.41	139.63 ± 26.88	.359	0.720

Table 3: Laboratory parameters between the two studied groups.

	Cases (n=50)	**Control (n=50)**	**MU**	**P**
IgM antibody titer (U/ml) Mean ± SD	1.93 ± 1.66	1.06 ± 1.28	891	**0.013**
IgM antibody titer in primigravida (U/ml) Mean ± SD	2.89 ± 1.63	1.52 ± 0.917	82	**0.009**
IgM antibody titer in multigravida (U/ml) Mean ± SD	1.19 ± 1.27	0.863 ± 1.37	363	0.080
IgM seropositivity				
Positive	26 (52%)	12 (24%)	**8.32**	**.004**
Negative	24 (48%)	38 (76%)		

Table 4: Helicobacter pylori results between the two studied groups.

DISCUSSION

Hyperemesis gravidarum (HG), the severest shape of gestation accompanying nausea and vomiting, is causing losing of weight, nutritional shortages, and metabolic disturbances, e.g., dehydrations, acidosis from starvations, hypokalemia, and transient hepatic dysfunctions, frequently needing hospital-stay and medical treatments to prevent deadly complication [7].

H. pylori, as a gram-negative flagellated spiral bacterium, colonize abdomen and create the base of gastric pathologies, involving chronic gastritis, duodenal and stomach ulcers, stomach adeno-carcinoma, and mucosa-connected lymphoid tissues lymphomas [8].

H. pylori infecting the stomach of half of the universal populations, and it are more dominant in developing republics [9]. The rate of prevalence of H. pylori infections in gravid females differs in accordance to socio-economic environments, geographic zone, and even the way utilized for H. pylori infections testing.

Numerous researches have revealed a probable participation of H. pylori infections in HG-cases; but other researches didn't share with them.

So the current work pointed to detect The Relationship among H. pylori infections and HG during pregnancy.

This case-control investigation included 100 pregnant women at 6-18 week of gestation who attended to AlZahraa University Hospitals outpatient clinics during the study period from March 2021 till the end of the study. Women have been allocated into 2 groups: Cases group which involving 50 gravid females with emesis gravidarum and controls which involve 50 ordinary gravid females.

In this study, both groups were comparable in basic demographic data as age, parity and GA. While a significant change was found among the study groups in regard to hemoglobin and MCHC which were significantly low among patients in comparison with controls.

In the current study, IgM anti-body titer was highly significant in cases in comparison with control-gorup. Moreover, IgM seropositivity was significantly more common in patients (52%) patients in comparison with controls (24%) with p value 0.004.

This is in agreement with Osama et study in which, 200 pregnant females from 6 to 18 weeks were subjected to detailed history, physical examination, ultrasonography and H. pylori IgG assay by ELISA. 100 pregnant females were complaining of emesis gravidarum group (A) and 100 pregnant females were not complaining of emesis gravidarum group (B). a highly significant change among group-A and -B as the mean IgG titers values in group (A) was (47.02) but in group (B) the mean was (24.97). Also, 68 cases (68%) in group (A) were seropositive and 32 cases (32%) were seronegative while in group (B) 60 cases (60%) were seropositive and 40 cases (40%) were seronegative [1].

This finding is identical to literature concluding a seropositive rate >68% H. pylori infections in cases with emesis gravidarum. A case-control research was done by Mai et al. 18 on Egyptian hyperemesis patients and healthy pregnant ladies. It showed a significant correlation among H. pylori infections and HG, where 84.4% were H. pylori positive and 15.6% were negative.

This result agrees with several reports performed by Jamal et al. [10] Frigo et al. revealed that the mean of

H. pylori IgG titer values in emesis group was 74.2 and in controls was 24.3 ($p<0.01$).

Kocak et al. concluded that the mean of H. pylori IgG titer values in emesis group was 73.8 and in controls was 25.8 (p-value<0.01) [11].

Jamal et al. revealed that the mean IgG antibody titer in emesis-group was 25 in comparison with 10.5 in controls (P-value<0.05) [10].

A metanalysis proposed that exposures to H. pylori is accompanying with a raised risk of HG. The metanalysis comprised researches, comprising 1851-cases with HG of which 1289-patients have been established with H. pylori infections, implied that the H. pylori infections rate was higher in HG-cases (1289/1851) in comparison to that in non-HG-cases (1045/2262) thereafter regulating for confounding parameters (P-value < 0.001) [12].

Sandven et al. involved 25 case-control researches involving 1455-HG cases and 1970-controls and performed sub-groups analyzing on corresponding design with non-matched one and Turkish people with other populations and found significantly higher H. pylori infection with HG groups [13].

Via PCR with sample of saliva, Güngören et al. revealed a positive association among the signs of HG and H. pylori positivity, whereas H. pylori IgG/IgM anti-body testing unsuccessful for detecting this correlation among the signs of HG and H. pylori positivity [14].

From biopsies of the stomach antrum and corpus, Bagis et al. revealed that, in comparison with control group, HG cases have been diagnosed with elevated H. pylori densities, degree of inflammatory, and H. pylori activations, suggesting that H. pylori densities may be connected to HG as the bacterium densities of control group was lower. These findings proposed that the gastric complaint degree may be connected to H. pylori density [15].

Sandven et al. as well reported this correlation among H. pylori infections and HG was much greater in Africans in comparison with non-africans [16].

Also reported, the rate of H. pylori infections prevalence is very high in developing republics in comparison to developed republics [17]. As Eshraghian studied, the total H. pylori infections prevalence in Iran and other Eastern Mediterranean Regional Office republics like Egypt and Afghanistan, regardless of times and ages group, ranging between 30.6 and 82% and ranging between 22 and 87.6%, respectively. But the prevalence of H. pylori in the North of Africa was 76 %[9]. The prevalence is higher in developing republics, whereas gravid females with HG in these republics have elevated rates of H. pylori infections. For instance, it is 50 to 70-% in Turkey [9], more than 80-% in Egypt [18]. The above researches all proposed that H. pylori infections was HG risk-factor.

While high rates of seropositivity for H. pylori in patients with emesis gravidarum was revealed, Khayati et al. reported no association among the onset and duration of signs and seropositivity in the HG group. The results done by Khayati et al. may mirror either the attendance of basic mechanism other than H. pylori in exacerbating emesis gravidarum, or the complicated nature of the H. pylori infections connected signs [19].

This is reliable with findings of Erdem et al. and Hayakawa et al. whose research failed to reveal an association among seropositivity for H. pylori in emesis gravidarum and the severity of clinical symptoms. Future studies may elucidate the association of emesis gravidarum and H. pylori [20].

Also females contributed in the current work weren't given H. pylori eradication regimens throughout gestation. In addition, we found seropositivity was high in both groups as cases seropositivity was (52%) and in controls was (24%).

This may be due to lack of demographic data like socio-economic condition that can be a risk-factor for H. pylori infections [21]. But most of the contributors who admitted to hospital in the studied groups (patients and controls) belonging to the low socio-economic classes. So, this parameter cannot impact the findings of this work, and the rate of H. pylori was elevated in the two groups. Moreover, it is familiar that H. pylori infections is a mutual human infection in the world that can be 90% in developing republics and the mainstream of patients still symptomless [22].

Our study proposed that H. pylori infections was a HG risk-factor. Frigo et al. proposed that the H. pylori can participate to its perseverance beyond the ordinary time courses [23]. It was primary revealed that HG was an oxidative-stress condition persuaded via an increase in reactive-oxygen species (ROS) activity and reducing anti-oxidant status [24]. In the meantime, H. pylori colonizes stomach mucosa and produces ROS in addition to down-regulating level of plasma anti-oxidants like ascorbic acid, identical to Güney et al. revealed that, in comparison with the controls, levels of serum malondialdehyde (MDA) was highly significant and activities of anti-oxidant enzymes like super-oxide dismutase (SOD), catalase (CT), and glutathione peroxidase (GSH-Px) were low significance in the HG-group (P-value < 0.01) [25].

Consequently, they assumed that the raised ROS activity or reduced anti-oxidant potentials, maybe persuaded by H. pylori, may have pathogenic functions in HG. Till now, but the awareness of how H. pylori cause HG is still very restricted, and we supposed the subsequent. First, hormonal mechanism, in the primary phases of gestation, as a consequence of the raised steroids and human

chorionic gonadotropins (HCG) level, buildup of fluids, and a dis-placement of intra-cellular and extra-cellular size happen which in order cause a shift in pH in the gastro-intestinal area throughout gestation [26].

Secondly, emotionally parameters, the moods of gravid females vary regularly because of the variations of endocrine hormone that may rise females' exposure to infections produced by changed cell-intermediated immunity that leads to variations of different types of anti-bodies throughout various pregnancy stages [24].

Third, H. pylori infections can be one possible cause for HG. Dysmotility of gastro-intestinal tract and extended gastric emptying and intestine transit period persuaded by gestation may favor H. pylori infections [27].

In contrast, host inflammatory responses to differs of virulency of H. pylori strains as well various shape each other. The virulency of the organism may be additional parameter producing a probable connection amongst H. pylori and the precipitations of HG. As we recognize, cytotoxin-accompanied gene A (CagA) products and vacuolating cytotoxin A (VacA) are utilized as indicators for genome variety of H. pylori. In Western republics VacA, instead of CagA, was related with more severe disorders, while in East Asian republics it is the reverse [28].

Probable clarifications for the propensity of H. pylori to lead to nausea and vomiting can be anomalous stomach discharging, decreased gastro-intestinal motilities in pregnancy and hyper-sensitivity to duodenal or gastric distention [29].

Fujiyama et al. concluded that eradication of H. pylori accelerate gastric discharging and post-prandial gastric sensations [30], whereas Rhee et al. cannot display these impacts [31]. But since nausea and vomiting in gestation as well occur in the nonattendance of H. pylori colonization, this proposes that the existence of the bacteria isn't obligatory for the nausea and vomiting inductions in gestation.

In the current work, IgM anti-body titer in primigravida was highly significant in patients relative to controls. However, IgM antibody titer in multigravida was higher in cases than controls but without statistical significance difference.

Kosunen et al. reported that detections of H. pylori IgG by CBC or serum-built serologic examinations cannot mirror present active infections as anti-bodies are positive for many months or even years afterward infecting [32]. Furthermore, since anti-body titer vs. H. pylori can be raised for many months afterward effective eradication, this can rise the incorrect-positives rates. But the serology examination is still extensively utilized for primary diagnosing previous to eradication treatment [29].

This confirms the correlation among H. pylori infections and hyperemesis as IgG was higher in multigravida which indicates their previous infection, while our study estimates the recent infection only.

This study had some restrictions to be acknowledged. First, our study design was case control, prospective and follow up study design will be much stronger. Second, the study didn't include the drug used during pregnancy which might be source of bias.

CONCLUSION

The current work proposed that a correlation was found among H. pylori infections and HG, permitting us to report that H. pylori must, consequently, take into consideration as a risk-factor of HG.

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