A meta-analysis of the association between Helicobacter pylori (H. pylori) infection and hyperemesis gravidarum

Qin Xiang Ng1,2 | Nandini Venkatanarayanan3 | Michelle Lee Zhi Qing De Deyn4 | Collin Yih Xian Ho2 | Yin Mo5 | Wee-Song Yeo5,6

1KK Women’s and Children’s Hospital, Singapore City, Singapore
2MOH Holdings, Singapore City, Singapore
3Queen’s Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK
4School of Medicine, Trinity College Dublin, Dublin, Ireland
5National University Hospital, National University Health System, Singapore City, Singapore
6Yong Loo Lin School of Medicine, National University of Singapore, Singapore City, Singapore

Correspondence
Qin Xiang Ng, KK Women’s and Children’s Hospital, Singapore City, Singapore.
Email: ng.qin.xiang@u.nus.edu

Abstract

Background: Hyperemesis gravidarum remains a common, distressing, and significant yet poorly understood disorder during pregnancy. The association between maternal Helicobacter pylori (H. pylori) infection and hyperemesis gravidarum has been increasingly recognized and investigated. This study thus aimed to provide an updated review and meta-analysis of the topic.

Methods: Using the search terms (H. pylori OR Helicobacter OR Helicobacter pylori OR infection) AND (pregnancy OR emesis OR hyperemesis gravidarum OR nausea OR vomiting), a preliminary search on the PubMed, Ovid, Web of Science, Google Scholar, and WanFang database yielded 372 papers published in English between January 1st, 1960 and June 1st, 2017.

Results: A total of 38 cross-sectional and case-control studies, with a total of 10 289 patients were eligible for review. Meta-analysis revealed a significant association between H. pylori infection and hyperemesis gravidarum during pregnancy, with a pooled odds ratio of 1.348 (95% CI: 1.156-1.539, \( P < .001 \)). Subgroup analysis found that serologic and stool antigen tests were comparable methods of detecting H. pylori as they yielded similar odds ratios.

Limitations: Although the studies did not have high heterogeneity \( (I^2 = 28\% ) \), publication bias was observed, and interstudy discrepancies in the diagnostic criteria adopted for hyperemesis gravidarum limit the reliability of findings. Also, 15 of the included studies were from the same country (Turkey), which could limit the generalizability of current findings. The prevalence of H. pylori infection varies throughout the world, and there may also be pathogenic differences as most strains of H. pylori in East Asia carry the cytotoxin-associated gene A gene.

Conclusion: H. pylori infection was associated with an increased likelihood of hyperemesis gravidarum during pregnancy. Given the high prevalence of H. pylori infections worldwide, detecting H. pylori infection and the eradication of maternal H. pylori infection could be part of maternal hyperemesis gravidarum management. Further confirmation with robust longitudinal studies and mechanistic investigations are needed.

Keywords
extragastric, helicobacter, hyperemesis gravidarum, infection, meta-analysis, pregnancy
Several pathological models of HG have been proposed, including maternal endocrine factors such as high human chorionic gonadotropin (hCG) levels, placental dysfunction, and gastrointestinal disorders. In recent years, the association between maternal *Helicobacter pylori* 

(H. pylori) infection and HG has been increasingly recognized and investigated. H. pylori is a prevalent gram-negative flagellated spiral bacterium that colonizes the stomach of half of the world’s population. It is responsible for gastrointestinal diseases such as ulcers and adenocarcinoma pathogenesis. Researchers have hypothesized that maternal hormonal and immunological changes during pregnancy that prevent allogenic rejection of the fetus reactivates the bacterium. Local inflammation and production of toxins by the bacterium contributes to the extensive vomiting in HG. Other urogynecologic disorders related to H. pylori infection (its pathogenic strain, ie, cytotoxin-associated gene A [CagA]-positive) include male and female infertility, maternal preeclampsia, and small-for-age newborns. The CagA gene codes for a major H. pylori virulence protein. H. pylori strains that produce high levels of CagA proteins are implicated in peptic ulceration and cause greater tissue damage than those that produce lower levels or that lack those genes completely.

Studies illustrating the link between H. pylori infection and HG, however, have been conflicting. Several new studies have been reported since the last meta-analysis conducted on this topic in 2014. Therefore, the current meta-analysis aims to provide an updated review of the subject and generate hypotheses for further research.

### 1 INTRODUCTION

Nausea and vomiting is a commonly occurring early pregnancy disorder, affecting around 80% of pregnancies. Most women remain well despite these unpleasant symptoms. However, 0.3%-2.0% of these women experience a more severe manifestation of this, known as hyperemesis gravidarum (HG). Unequivocal diagnostic criteria for HG is lacking, but many of the definitions include a constellation of symptoms, including protracted nausea and vomiting, weight loss, dehydration, electrolyte disturbances, and ketonuria. HG accounts for the most common cause of hospitalization in early pregnancy.

Suffering from HG puts both the mother and fetus at risk of adverse outcomes. Numerous studies have illustrated the association of HG with low birthweight, preterm birth, and small-for-gestation age infants. Additionally, few retrospective studies have also reported behavioral disorders in offsprings of patients with HG. This disease is both physically and psychologically debilitating for the mother. If not adequately managed, HG can lead to electrolyte disorders, malnutrition, end-organ damage, and Wernicke’s encephalopathy in severe cases. Large prospective studies have highlighted that mothers with HG are prone to suffer from depression and post-traumatic stress disorders. Even with its low prevalence, because of the severity and long-term fetal and maternal effects of HG, this disease still imposes a large socioeconomic cost.

The lack of reliable diagnostic markers for HG means that clinical judgment plays a vital role in its diagnosis. This introduces subjectivity, thereby often causing a diagnostic delay. Coupled with the fact that treatment options for HG are mainly symptomatic alleviation including fluid replacement and anti-emetics, the diagnosis and management of HG remain suboptimal.
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<td>Bagis, 2002</td>
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<td>Endoscopy with biopsy and histology</td>
<td>19.00 (1.79, 201.68)</td>
<td>Main findings of pangastritis and enterogastric reflux on endoscopy are associated with H. pylori infection, confirmed histologically. Increased density of infection is associated with more severe symptoms.</td>
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<td><em>H. pylori</em> infection is associated with symptoms of hyperemesis.</td>
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<td>Karadeniz,</td>
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<td>Serum IgG by ELISA</td>
<td>0.55 (0.17, 1.77)</td>
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<td>3.64 (1.52, 8.73)</td>
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<td>Case control</td>
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<td>Turkey</td>
<td>Vomiting &gt;3 times/day Ketonuria</td>
<td>Serum IgG by FEI</td>
<td>13.38 (5.95, 30.13)</td>
<td>More pregnant women with hyperemesis are infected with <em>H. pylori</em> than control group.</td>
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<td>Lee, 2005</td>
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<td>Vomiting &gt;3 times/day Weight loss &gt;3 kg Ketonuria</td>
<td>Serum IgG by ELISA</td>
<td>0.93 (0.37, 2.31)</td>
<td>Infection with <em>H. pylori</em> does not increase the risk of suffering from HG.</td>
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<td>Mansour, 2009</td>
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<td>Vomiting &gt;3 times/day Weight loss Ketonuria</td>
<td>Serum IgG by ELISA</td>
<td>9.33 (3.60, 24.17)</td>
<td>Significant association between <em>H. pylori</em> infection and HG.</td>
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<tr>
<td>Mansour, 2011</td>
<td>Case control</td>
<td>160 Egypt</td>
<td>Vomiting &gt;3 times/day Weight loss &gt;3 kg Ketonuria</td>
<td>Serum IgG by ELISA</td>
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<td>Vomiting &gt;3 times/day Weight loss &gt;3 kg Ketonuria</td>
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<td>Sadek, 2017</td>
<td>Case control</td>
<td>80 Egypt</td>
<td>Vomiting &gt;3 times/day Weight loss &gt;5% Ketonuria</td>
<td>Serum IgG by ELISA and stool antigen</td>
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<td>Significant association between <em>H. pylori</em> infection and HG.</td>
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<td>Sahin, 2000</td>
<td>Case control</td>
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<td>Prolonged severe vomiting Dehydration Weight loss &gt;5% Ketonuria</td>
<td>Serum IgG by ELISA</td>
<td>1.41 (0.68, 2.91)</td>
<td><em>H. pylori</em> infection should only be considered refractory cases of hyperemesis.</td>
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<td>Salimi-Khayati, 2003</td>
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<td>Serum IgG by ELISA</td>
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<td>No causal relationship between <em>H. pylori</em> infection and hyperemesis noted.</td>
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<td>Sandven, 2008</td>
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<td>Serum IgG by ELISA</td>
<td>2.42 (1.64, 3.57)</td>
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<td>Shaban, 2014</td>
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<td>Vikanes, 2013(^{57})</td>
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<td>Serum IgG antibodies and CagA and VacA by EIA</td>
<td>0.97 (0.51, 1.84)</td>
<td>Infection with H. pylori is not a risk factor for suffering from hyperemesis during pregnancy.</td>
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<td>Xia, 2004(^{48})</td>
<td>Case control</td>
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<td>China</td>
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<td>Serum IgG and CagA by ELISA</td>
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<td>The prevalence of H. pylori was 88.9% and 45.0% among patients with HG and control subjects, respectively.</td>
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<td>Yasmin, 2016(^{49})</td>
<td>Cross-sectional</td>
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<td>Bangladesh</td>
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<td>Serum IgG by ELISA</td>
<td>3.85 (1.43, 10.34)</td>
<td>Significant association between H. pylori infection and HG.</td>
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CagA, cytotoxin-associated gene A; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HG, hyperemesis gravidarum; VacA, vacuolating cytotoxin A.
consensus among the 3 researchers. The inclusion criteria for this review were as follows: (1) published case-control or cross-sectional study, (2) subjects with clinical diagnosis of HG (as defined by authors), and (3) confirmed/laboratory testing for presence of *H. pylori*.

Data such as study design, study population and demographics, and outcome measure were extracted. The primary outcome measure of interest was the proportion of *H. pylori* infection in patients with HG compared to a control group. Odds ratio were calculated for each study.
individual study. Estimates were pooled and where appropriate, 95% confidence intervals (95% CI) and P-values were calculated.

Heterogeneity among the different studies pooled was examined using the I² statistic and Cochran’s Q test. Publication bias was assessed using a funnel plot and Egger test. All analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014) and Stata version 13.0 (2000; STATA Corp., College Station, TX, USA).

3 | RESULTS

The key details of each study are extracted and summarized in Table 1.

With regard to the possibility of publication bias, visual inspection of the funnel plot revealed an asymmetrical distribution of studies (Figure 2) and Egger test was significant for publication bias (P < .0001).

The meta-analysis found that H. pylori infection was associated with an increased likelihood of HG during pregnancy (pooled OR 1.348, 95% CI: 1.156-1.539, P < .001) (Figure 3). A separate subgroup analysis was conducted to analyze the effect of the method of H. pylori detection on the association between H. pylori infection and HG, comparing the 2 main methods utilized, that is, serum IgG antibodies and stool antigen assay. It was found that both methods of detection yielded similar results, with a pooled odds ratio of 1.518 (95% CI: 1.178-1.859, P < .001) and 1.463 (95% CI: 0.689-2.237, P < .001) for the serum antibody and stool antigen assay, respectively (Figures 4 and 5).

4 | DISCUSSION

Current evidence suggests that H. pylori infection is associated with an increased likelihood of HG during pregnancy (pooled OR 1.348, 95% CI: 1.156-1.539, P < .001). These results were concordant with the last meta-analysis conducted on this topic in 2014 by Li et al, which reported a pooled OR of 3.34 (95% CI: 2.32-4.81, P < .001). Although the OR appears more modest, the current meta-analysis included a further 8 studies (with a total of 6081 patients recruited) and had a much lower overall heterogeneity (I² = 28% vs 81.5%) and smaller 95% confidence intervals. This thus strengthens the association between H. pylori infection and HG.

A clear pathogenesis of HG is yet to be defined. However, the current school of thought is that HG is an end product of the complex interplay of different unrelated disorders. Pregnancy-induced metabolic, endocrine, and immunological changes in a genetically predisposed woman make her more susceptible to suffer from HG. Additionally, social factors such as poor nutrition and psychological disturbances contribute to the pathogenesis. This study has identified a further cause, H. pylori infection, to the pathological model of HG. Unlike the other known causes of HG, this is a pivotal finding as it opens up diagnostic and treatment options for the disease.

Pregnancy causes immunological changes in a woman that prevent rejection of the semi-allogenic fetus. These changes include a diminished cell-mediated immunity, hence making her more prone to infections, such as H. pylori. The infection can be primary or re-activated latent infection. Lanciers et al illustrated a high incidence of H. pylori IgM antibodies, a marker of recent infection, in pregnant women compared to nonpregnant women, thereby proving the notion that pregnancy itself is a risk factor for H. pylori infection. Once infected, the bacterium colonizes antral gastric mucosa, produces toxins that induce mucosal damage, and causes local inflammation. This gastrointestinal alteration during pregnancy then potentiates the protracted nausea and vomiting in HG. Interestingly, a study by Xia et al shows that CagA seropositive H. pylori infection dominates pregnant women. The CagA toxin is injected into the gastric epithelial cells and induces apoptosis by causing cell morphological changes. The heightened inflammatory response associated with CagA seropositive infection poses as a potential reason for the severity of symptoms associated with HG.

The association between HG and H. pylori infection is of immense clinical significance as it presents new diagnostic and therapeutic approaches to the disease. H. pylori infection is also extremely prevalent globally, with an estimated 4.4 billion infected individuals in 2015. Further reasons to support H. pylori testing during the workup of pregnancy include the fact that H. pylori infection is also well associated with male and female infertility, maternal preeclampsia, and small-for-age newborns. Currently, there are no universally accepted diagnostic criteria for HG. It is a clinical diagnosis based on patient account of symptoms and the exclusion of other conditions that could cause severe nausea and vomiting, such as hepatobiliary disease and acute severe infections. Treatment options for HG currently focus on symptomatic alleviation including fluid replacement and anti-emetics. The detection of H. pylori in pregnant women presenting with these symptoms would not only support a clinical diagnosis of HG but also provide a treatment strategy for the disease.

Although they provide definitive diagnosis, invasive tests such as upper gastrointestinal endoscopy with gastric mucosal biopsy for histopathologic detection of H. pylori are unfavorable in pregnant women. Therefore, noninvasive methods of diagnosis such as serum antibody detection, urea breath test, and stool antigen detection are the mainstay tests of choice. Detection of anti-H. pylori IgG antibodies in a patient’s serum through enzymatic immunoassay could represent current or previous infection as the antibodies persist for several months, or even years after eradication. Stool antigen test detects active infection and is usually the test of choice to monitor H. pylori status after eradication. Though supported by little evidence, the 13-C urea breath test is not routinely used in pregnancy due to fears of the 13-C isotope being radioactive. Therefore, IgG antibodies could be used to detect H. pylori infection in patients presenting with HG while post eradication monitoring of infection could be carried out by stool antigen testing.

Eradication of H. pylori in infected pregnant women can significantly improve symptoms in HG as illustrated by several case-control studies. There is no clear clinical guideline for the eradication of H. pylori in pregnancy. Treatment options include the utilization of triple therapy, consisting of a proton-pump inhibitor and 2 antibiotics.
such as amoxicillin and metronidazole for 2 weeks.\textsuperscript{61} However, pharmacological interventions must be used with caution in pregnancy due to the possibility of teratogenicity. A recent meta-analysis reported that proton-pump inhibitors such as omeprazole are not associated with fetal malformations.\textsuperscript{62} Additionally, amoxicillin and metronidazole do not fall into the classes of antibiotics that are known to be teratogenic.\textsuperscript{63} Nonetheless, current studies investigating the use of triple therapy in pregnancy only examined a small number of patients. Furthermore, the use of proton-pump inhibitors in early pregnancy remains contentious as animal experiments in developing Xenopus and chicks have found the H\textsuperscript{+}/K\textsuperscript{-} ATPase transporter essential for the early segmentation of the gastrula.\textsuperscript{64} Therefore, large-scale studies on the usage of triple therapy for eradication of \textit{H. pylori} are required to confirm the safety and efficacy of this treatment in pregnancy.

Interstudy discrepancies in the diagnostic criteria utilized for HG limit the reliability of this meta-analysis. Additionally, tests used to detect \textit{H. pylori} infection are not uniform in the studies included in this analysis, thereby impacting the results. However, our subgroup analysis found that the 2 main methods of \textit{H. pylori} detection, that is, serum IgG antibodies and stool antigen assay, yielded similar results, with a pooled odds ratio of 1.518 (95\% CI: 1.178-1.859, \textit{P} < .001) and 1.463 (95\% CI: 0.689-2.237, \textit{P} < .001), respectively. This was concordant with the findings of studies that utilized both methods in a single study.\textsuperscript{24,37,40} although one study\textsuperscript{18} only found a significant association between \textit{H. pylori} detection and HG for stool antigen results and not seropositivity. The authors of the study\textsuperscript{18} attributed this discrepancy to the fact that a positive serologic test is unable to differentiate between current infection and a previous exposure. As previously discussed, the serologic test is unreliable as it remains positive for even years, after recovery from \textit{H. pylori} infection.

Many of the available studies also did not adjust for potential confounders, for example, poor socioeconomic status is associated with both \textit{H. pylori} infection and HG. Other limitations of current evidence include the fact that 3 of the 38 studies performed anti-CagA testing. This must be stressed. Also, 15 of the included studies were from a single country—Turkey, which could limit the generalizability of current findings. The rate of \textit{H. pylori} infection varies throughout the world. The prevalence of \textit{H. pylori} is estimated to be around 80\% in Turkey,\textsuperscript{65} and it is higher in many developing countries, with the prevalence of infection exceeding 90\% by adulthood.\textsuperscript{66} There may also be pathogenic differences between Western and Eastern countries as most strains of \textit{H. pylori} in East Asia carry the CagA gene.\textsuperscript{57} Moreover, some of the studies utilized only a single assay for detection of \textit{H. pylori} presence, and as aforementioned, not all available tests can detect the infection with sufficient accuracy.

Given the significant physical, psychological, and economical burden HG imposes, quality research to allow better understanding of its pathophysiology, diagnosis, and treatment is paramount. A universally accepted diagnostic criterion for HG is firstly required to conduct reliable research on this topic. Additionally, longitudinal studies investigating the identification of \textit{H. pylori} infection in women with HG, eradication of the infection with triple therapy during pregnancy, and its effect on the disease course of HG and fetal outcomes need to be conducted to truly understand the significance of this association. In a disease with limited understanding and treatment options, this meta-analysis has definitely opened up new avenues for research that could significantly impact current clinical practice.

5 | CONCLUSION

\textit{H. pylori} infection was associated with an increased likelihood of HG during pregnancy, with a pooled OR of 1.348 (95\% CI: 1.156-1.539, \textit{P} < .001) based on 38 case-control and cross-sectional studies and a total of 10 289 patients. Given the high prevalence of \textit{H. pylori} infections worldwide,\textsuperscript{52} and the other urogynecologic disorders related to \textit{H. pylori} infection,\textsuperscript{6-9} detecting \textit{H. pylori} infection during the workup of pregnancy and the eradication of maternal \textit{H. pylori} infection could be part of maternal HG management. Serologic and stool antigen tests appear comparable methods of detecting \textit{H. pylori}. Looking forward, new avenues of research into the diagnosis and management of this disease should be explored. Longitudinal studies investigating the detection of \textit{H. pylori} infection in women with HG, eradication of the infection with triple therapy during pregnancy, and its effect on the disease course of HG and fetal outcomes should be conducted to better elucidate the significance of this association. Further detailed studies on CagA-positivity and HG should be considered, as the grade of systemic inflammation may influence the severity of symptoms.

DISCLOSURES OF INTEREST

The authors report no conflict of interests. The authors alone are responsible for the content and writing of the article.

AUTHORS’ CONTRIBUTIONS

Qin Xiang Ng conceived, designed, and carried out the study, and analyzed and interpreted the relevant data. Nandini Venkatarayanan, Michelle Lee Zhi Qing De Deyn, and Collin Yih Xian Ho carried out the study, analyzed, and interpreted the relevant data. Yin Mo and Wee-Song Yeo contributed to the data interpretation. All authors discussed the results and contributed to the writing and proofreading of the final manuscript.

ORCID

Qin Xiang Ng \href{http://orcid.org/0000-0001-8561-2513}{http://orcid.org/0000-0001-8561-2513}

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