# Relationship between Helicobacter Pylori Infection and Preterm Labor

# A Case-Control Study

**Thesis**

*Submitted for fulfillment of M.Sc. Degree in Obstetrics & Gynecology*

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**2019**

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# List of Abbreviations

| | |
|---|---|
| CagA | Cytotoxic associated gene A |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| DNA | Deoxyribonucleic Acid |
| ELISA | Enzyme Linked Immunosorbent Assay |
| FDA | Food and Drug Administration |
| FGR | Fetal Growth Restriction |
| FW | Fetal Weight |
| GA | Gestational Age |
| GDM | Gestational Diabetes Millets |
| GI | Gastrointestinal |
| H. pylori | Helicobacter pylori |
| Hb | Hemoglobin |
| HELLP | Hemolysis, elevated liver enzymes and low platelet count syndrome |
| HG | Hyperemesis Gravidarum |
| HLA | Human Leucocyte Antigen |
| IDA | Iron Deficiency Anemia |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| iNOS | Inducible Nitric Oxide Synthase |
| IUGR | Intrauterine Growth Restriction |
| LDL | Low Density Lipoprotein |
| LPS | Lipopolysaccharide |
| MALT | Mucosal Associated Lymphoid Tissue |

| | |
|---|---|
| NIH | National Institute of Health |
| NSAIDs | Non-steroidal Anti-inflammatory Drugs |
| OMPs | Outer Membrane Proteins |
| PAF | Platelet Activating Factor |
| PE | Preeclampsia |
| PMNs | Polymorphonuclear cells |
| PROM | Prelabor Rupture of Membranes |
| PTL | Preterm Labor |
| ROS | Reactive Oxygen Species |
| rRNA | Ribosomal Ribonucleic Acid |
| SEM | Scanning Electron Micrograph |
| SGA | Small for Gestational Age |
| TNF | Tumour Necrosis Factor |
| UBT | Urea Breath Test |
| Vac A | Vaculating toxin A |
| WHO | World Health Organization |

# 1. Introduction

Various gastrointestinal diseases, such as gastric mucosal-associated lymphoid tissue lymphoma, gastric adenocarcinoma, and peptic ulcer disease, have been directly connected to *Helicobacter pylori* (*H. pylori*), a Gram-negative bacteria occurring in the stomach ***(Conteduca et al., 2013)***.

Pursuing the public health studies' observations, though, *H. pylori* was proposed to be correlated with many additional gastrointestinal diseases ***(Suzuki et al., 2011),*** hematological cardiovascular disease ***(Niccoli et al., 2010)*** and ***(Franceschi et al., 2014),*** disease (unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura) ***(Arnold et al., 2009),*** and neurological disorders ***(Roubaud-Baudron et al., 2012).***

Nowadays, many researches on the obstetric field gave a considerable attention to potential influence of *H. pylori* infection in pregnant female. Females who were experienced preeclampsia within pregnancy, exhibited high prevalence of the *H. pylori* (***Cardaropoli et al., 2011)***. Furthermore, a particular gastrointestinal symptom, hyperemesis gravidarum, was also connected to *H. pylori* ***(Cevrioglu et al., 2004)***.

Owing to the above-mentioned observations, a concern arose to know in precise the *H. pylori* infection status for female in gestational age. Many methods have been reported to detect *H. pylori* infection. Urease test utilizing mucosal tissue acquired during gastro endoscopy is one of these methods. Although it was proven that this method is safe for the pregnant women ***(Winbery et al., 2001)***, it is still can't be considered an ideal choice for checking the *H. pylori* infection during pregnancy due to the invasiveness of the procedure, the general unwillingness, the possible

sampling error, and the high cost. On the other hand, the noninvasive tests include the stool antigen test, the urea breath test (UBT), and the serum *H. pylori* IgG antibody test. The latter is facile to proceed throughout antenatal examination and the existence of the antibody was found to be related to the intrauterine growth restriction ***(Eslick et al., 2002)***.

## 2. Aim of the Work

This study aims to investigate the association between *H. pylori* infection and preterm labor.

# 3. Review of Literature

## 3.1. Helicobacter Pylori

### 3.1.1. Detection of *H. Pylori* and historical progress of its role in human disease

In 1979, it was noticed by Robin Warren, a pathologist in Perth, Western Australia, that curved bacteria were predominantly existed in gastric biopsy samples submitted for histological screening. These curved bacteria were not identified within the gastric mucosa but were observed in the mucus layer overlying the tissue ***(Marshall, 1989).***

Warren noticed that comparable microorganisms had been reported in the late 19th century by European pathologists, but due to isolation difficulties, they were basically forgotten and neglected by generations of scientists and physicians ***(Warren et al., 1983)***.

Later, Barry Marshall, an internal medicine young trainee, gave a special attention to Warren's work, and thoroughly explored the possibility of the bacteria isolation from the biopsy specimens. The investigators utilized the methods used to isolate *Campylobacter* species, as the organisms under investigation exhibited the shape of curved gram-negative rods. The used method involved the inoculation of the biopsy specimens onto certain media then using microaerobic conditions to incubate the cultures ***(Marshall, 1989).***

It is well known that, using the above-mentioned conditions allows most of campylobacters to grow within 48 h, therefore any plates didn't reveal visible growth were discarded after 3 days. The initial cultures for about 30 patients were negative, but accidently and due to incubation for 5 days over an Easter holiday, colonies were observed in one culture.

Subsequently, the organism was isolated from 11 patients, characterized, and called *Campylobacter pyloridis* (currently known as *Helicobacter pylori*) ***(Marshall, 1989).***

After this crucial work, researchers worldwide asserted the existence of the new discovered organisms in the gastric mucus ***(Jones et al., 1984).***

In 1984, the inflammation in the gastric mucosa (chronic superficial gastritis), and especially with polymorphonuclear cell infiltration (chronic active gastritis) was strongly connected to *H. pylori* infection, despite, several years before, there was adequate evidence that an etiologic role could be concluded ***(Blaser et al., 1990).*** A massive body of evidences illustrate that once acquired, *H. pylori* persist, usually for life, unless antimicrobial therapy is used to eradicate it ***(Blaser et al., 1997).***

Moreover, Marshall and Warren reported that *H. pylori* infection was accompanied with duodenal ulceration ***(Warren et al., 1983)***, and this observation too was expeditiously proved and extended to comprise gastric ulceration ***(Blaser et al., 1987).*** Later, in 1994, a conference held by the National Institutes of Health had reached a consensus about that *H. pylori* was a main cause of peptic ulcer disease and proposed that individuals who are infected with ulcers should be treated to eradicate *H. pylori* ***(NIH Consensus Conference. 1994).***

The development of stomach adenocarcinoma, the most important gastric malignancy in the world, had been connected to chronic gastritis by many evidences ***(Correa et al. 1992)***, however the causation of the gastritis was then unidentified yet. In 1991, four different reports disclosed, for the

first time, the relation between *H. pylori* infection and the detection ***(Talley et al., 1991)*** or the development of gastric cancer ***(Parsonnet et al., 1991)***.

Three years later, and after reviewing the available evidences, it was declared by the International Agency for Cancer Research, an arm of the World Health Organization, that *H. pylori* is a human carcinogen ***(IARC 1994).***

Furthermore, the development of gastric non-Hodgkin's lymphomas has been linked to *H. pylori* infection as well ***(Parsonnet et al., 1994)*** in addition to another lymphoproliferative disorder, gastric mucosa-associated lymphoid tissue (MALT) lymphoma (MALToma) ***(Wotherspoon et al., 1991).***

Notably, regression of tumors was observed when patients with gastric MALToma were treated with antibiotics that eradicate *H. pylori* ***(Wotherspoon et al., 1993).*** Consequently, *H. pylori*, a previously ambiguous organism, has now been linked to a considerable number of the most substantial diseases associated with gastroduodenal tissue.

### 3.1.2 Epidemiology of *H. Pylori* Infection

#### 3.1.2.1 Descriptive Epidemiology

Interestingly, 70 to 90% of the population in developing countries carries *H. pylori* and most of them got infected before the age of 10 years ***(Taylor et al., 1995)***. On the other hand, the percentage of the infected individuals in the developed countries is lower and lies between 25 to 50%. Also, reports from developed countries suggesting that most of the infections were acquired in the childhood ***(Taylor et al., 1995).*** In the same context, it is proposed that the industrial development has a direct influence on declining

*H. pylori* infection ***(Parsonnet, 1995)*** and ***(Hooi et al. 2017)***. Therefore, in an age of "emerging" microbes, we might consider *H. pylori* as steadily "submerging" from presumably near-universality couple of hundred years ago to the current situation when less than 10% of children in developed countries are becoming infected ***(Vandenplas et al., 1992).*** Many studies proposed that the rate of infection for males and females are approximately the same, although one study suggested that male sex was a considerable risk factor for *H. pylori* infection ***(Replogle et al., 1995).*** Despite that fact that in developed countries people with high socioeconomic status reveled lower infection rates, high infection rates was observed within specific ethnic minorities, regardless the economic advancements ***(Graham et al., 1995).***

## *H. pylori* Transmission

The least prevalent method of transmission is iatrogenic, in which specimens, tubes, or endoscopes got in direct contact with the gastric mucosa of infected person are used for another person ***(Akamatsu et al., 1996).*** The improvement of disinfection techniques of endoscopes has considerably minimized the possibility of transmission ***(Tytgat, 1995).*** It is worth mentioning that endoscopists who did not use gloves during procedures were at higher risk of being infected ***(Mitchell et al., 1989).*** Also, occupationally obtained infections have been observed ***(Sobala et al., 1991)***, although it appears that there are no certain risks are correlated to the handling of this microbe, universal precautions should be utilized by laboratorians on handling clinical specimens as they dealing with human pathogens.

The most relevant method of transmission is Fecal-oral ***(Thomas et al., 1992)***. Contaminated water with fecal material is important source of

infection ***(Klein et al., 1991)***, although the microbe has not been isolated from water.

Finally, oral-oral transmission was observed in case of premasticated food given to infants by their African mothers ***(Megraud, 1995).*** There is no clear evidence of infection with sexual transmission ***(Polish et al., 1991).*** In conclusion, it is hard to understand how *H. pylori* transmitted, although different *H. pylori* strains are present in the stomachs of about half of the world's population.

**Association with Particular Diseases**

Almost all patients infected with *H. pylori* developed chronic gastric inflammation ***(Blaser et al., 1990)***, but this condition usually is asymptomatic.

Peptic ulcer disease had been considered to be either idiopathic or due to certain medications like nonsteroidal anti-inflammatory drugs or aspirin. Sometimes, and in rare cases, peptic ulcer disease was attributed to Crohn's disease, Zollinger-Ellison syndrome, or any other inflammatory disorder ***(Peterson, 1991).*** Obviously, of all cases, 60 to 95% of peptic ulcer disease is idiopathic (depending on the population nonsteroidal anti-inflammatory drug usage). Now, we could connect all these cases in adults to *H. pylori* and found that eradicating *H. pylori* curing the ulcers.

Consequently, in any population, the majority of all recorded cases of both duodenal and gastric ulcers are directly caused by *H. pylori*.

Development of atrophic gastritis is one of the risks associated with *H. pylori* carriage ***(Blaser et al., 1990)***, also adenocarcinoma of the distal but not

the proximal (cardia) stomach ***(Talley et al., 1991).*** Infection is connected to both the diffuse and intestinal histologic forms of tumors. This connection is considerably important as, in total, gastric cancer is the second major cause of cancer death worldwide ***(Neugut et al., 1996).***

Moreover, the rare gastric disease Menetrier's is also associated to *H. pylori* infection, in which the gastric folds are hypertrophic ***(Yasunaga et al., 1994).*** Patients with various group of upper gastrointestinal symptoms that has been described no ulcer dyspepsia may or may not have *H. pylori* infection. Currently, there is no direct known connection of any ulcer dyspepsia with *H. pylori* infection ***(Hunter et al., 1993).***

Although early reports associated *H. pylori* infection with heart disease ***(Patel et al., 1995)***, later reports proposed that this connection may have been confused with other factors ***(Sandifer et al., 1996).*** Also, short stature was linked to *H. pylori* infection but this finding has not been proved ***(Patel et al., 1994)***.

Finally, there is no known association of the chronic fatigue syndrome and *H. pylori* infection.