BAHRI UNIVERSITY

Faculty of Medicine (Microbiology Department)

The relation between Helicobacter pylori and Hyperemesis gravidarum

Thesis submitted for Fulfillment of PHD degree in Medical Laboratory science (Microbiology)

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Chapter 1

Introduction

1.1 Background

Does Helicobacter pylori cause nausea & vomiting in pregnancy?

Does hyperemesis gravidarum (HG) is a rare disorder characterized by severe nausea and vomiting?

Hyperemesis gravidarum (HG) is an intractable form of nausea and vomiting affecting approximately 0.3–2 % of all pregnancies (1). HG is associated with maternal and perinatal morbidity, often requiring hospitalization and medical treatment to avoid life-threatening complications (2).

Little is known about the etiology of HG, but a variety of mechanisms related to endocrine and immunologic factors, gastrointestinal conditions and metabolic enzymes have been proposed as possible underlying causes (3). Helicobacter pylori has been recognized to play a role in diseases of the gastrointestinal tract (4). It has been hypothesized that H. pylori may increase the risk of HG, examining the association between H. pylori and HG, we conducted an updated meta-analysis.

Pylori infection may increase the risk of HG might be explained by physiological changes in pregnancy and the virulence of the bacterium. First, gastric emptying and intestinal transit time may be prolonged during pregnancy due to elevated serum concentration of steroid hormones and their relaxant effects on gastrointestinal smooth muscle (6). Second, it has been assumed that pregnancy increases women's susceptibility to infections due to some form of immune depression in the mother to allow for the survival of the fetal semiallograft (7), and latent infections might be reactivated in pregnancy (8). Hypothetically, decreased gastrointestinal motility and a depressed immune defense during pregnancy could result in the manifestation of a sub-clinical H. pylori infection, which in turn irritates the gastrointestinal tract. Finally, the inflammatory response to H. pylori might be determined by the virulence of the infecting strain and the human host (5). Moreover, Further, it is interesting that antibiotics have relieved symptoms of nausea and vomiting in H. pylori positive HG patients (9-10).

1.2 Problem Statement

It is known that the Symptoms of Helicobacter Pylori is as same as the signs of Hyperemesis Gravidarum. Therefore it is somewhere of a complicated procedure to distinguish them apart from each other. The purpose of this scientific writing & research is to; distinguish whether the Helicobacter Pylori induce and increase the signs of Hyperemesis Gravidarum or if there is no connection between the two topics.

1.3 Justification

1/ Symptoms of H. Pylori infections can be similar to those of hyperemesis gravidarum. Comparisons may be useful for a differential diagnosis.

2/ Both are associated with nausea and vomiting.

3/ Both make problem such as general feeling of discomfort in the stomach.

4/ In both cases of hyperemesis gravidarum,and H. pylori drugs that may lessen nausea and vomiting can be prescribed.

1.4 Literature Review

Morning sickness is one of the typical symptoms of early pregnancy. It involves nausea and/or vomiting during the first few months of pregnancy. The name is somewhat misleading since nausea can actually set in at any time of the day. For many pregnant women, this symptom appears during the first trimester and it generally resolves by around the 12th or 14th week. Some, however, suffer from an extreme form of morning sickness that lasts throughout the duration of the pregnancy.

According to the National Health Services, UK, as many as 7980% of pregnant women experience nausea and vomiting. An estimated 1.5% of pregnant women suffer from a severe form of morning sickness known as hyperemesis gravidarum. Accurate statistics are hard to obtain because not all such women necessarily seek or receive formal diagnosis and treatment for this condition.

What Is Hyperemesis Gravidarum?

Some women suffer from a very severe form of morning sickness. Typically, this involves extreme nausea and excessive vomiting. The food that the woman does manage to eat may be vomited out soon after. As a result, the pregnant mother's body does not get the nutrition it needs both for its own maintenance as well as in order to support the development of the fetus.

This condition is generally severe enough to lead to significant weight loss, dehydration and electrolyte imbalance. It may leave the woman weak and unable to stand without feeling dizzy. Hence, she may become incapable of carrying out routine tasks by herself. This condition can last throughout the duration of pregnancy and can be so acute that the woman might require hospitalization. Although there is no cure for it, patients can tide over the symptoms with adequate rest, medications and support. This condition is a transient one that resolves when the pregnancy ends.

What Causes Hyperemesis Gravidarum?

It is unclear why some women suffer from extreme morning sickness whereas others do not. It is believed that hormonal changes associated with pregnancy might be responsible for giving rise to this condition. Specifically, the elevated quantities of estrogen and the pregnancy hormone called human chorionic gonadotropin have been blamed for this condition. It may also have to do with genetics to a certain extent.

The list below covers some risk factors that appear to have a bearing on this condition:

Some studies have found a correlation between hyperemesis gravidarum and infection with the bacterium Helicobacter pylori.

The risk of suffering from hyperemesis gravidarum is higher in instances where the fetus is female.

Women who have had multiple pregnancies are more likely to develop this condition.

First-time mothers are also at risk.

Those who are pregnant with more than one fetus are at risk as well.

What are the signs of hyperemesis gravidarum?

The symptoms of hyperemesis gravidarum tend to manifest sometime between the 4th and 6th weeks of pregnancy. They can range from moderate to debilitating in severity. It has also been noticed that some women with this condition develop transient hyperthyroidism. This means that they exhibit the signs of overactive thyroid function but that it lasts only as long as the pregnancy does and resolves soon after on its own. A more detailed list of symptoms associated with hyperemesis gravidarum appears below:

Severe nausea and vomiting. The vomiting may be triggered by strong smells.

Inability to keep food down after eating or fluids after drinking.

Developing aversion to certain foods.

Headaches, Loss of appetite, dehydration, Severe fatigue,
Reduced frequency and quantity of urine, Dizziness, Weight loss ,acidosis as a result of malnutrition Electrolyte imbalance such as hypokalemia (abnormally low levels of potassium in the blood), elevated heart rate Blood in vomit ,and fainting.

What Are Some Severe Outcomes Associated With Hyperemesis Gravidarum?

There can be a whole host of critical complications as a result of untreated hyperemesis gravidarum. This condition poses grave risks to the health of both the mother as well as the fetus. As a result, there can be severe pregnancy complications as well. In fact, in severe instances, the fetus could actually die.

How Is It Diagnosed?

Severe nausea, vomiting and the inability to tolerate ingested solids and fluids are the classic signs of this condition. Tests may be required in order to establish the extent of malnourishment and electrolyte disturbance as well as any adverse effects on fetal

development. There is no specific positive finding that definitively indicates hyperemesis gravidarum. Instead, depending on the symptoms displayed, the doctor may need to first rule out a variety of other possibilities .Some tests that can help to establish the diagnosis are listed below:

Physical examination. The woman may have lost upwards of 5% of her pre-pregnancy body weight.

Medical history.

Blood tests to check for electrolyte disturbance, acidosis or alkalosis for example.

Urine tests help to confirm hyperemesis in case of relevant findings such as low water concentration and the presence of ketone bodies in the urine.

Stool, serum ,urea breath test for detection of H.pylori infection.

What Can Be Done For Relief?

The treatment of hyperemesis gravidarum is chiefly based on your symptoms and the way it is affecting your health. It is estimated that around 5% of females require care in a hospital setting. other recommend such as the following:

Lifestyle changes– Try having frequent smaller meals instead of fewer large ones. Consume plenty of fluids sip by sip preferably using a straw. In case hot foods trigger nausea, try cold foods. Doctors may also recommend nutritional supplements and electrolyte-replacement sports drinks in order to manage dehydration and your nutritional needs.

Stress Management– Get enough sleep and keep stress at bay by learning methods to manage stress.

Vitamin B supplements- Thiamine or vitamin B1 is usually prescribed to ease vomiting. The prescribed dosage is 1.5 milligrams per day.

Ginger supplements- Ginger intake in small doses can help females with hyperemesis gravidarum. It can be consumed in various forms such as lollipops, tea, candies, supplements etc. It is advised to take around 1 to 1.5 grams of ginger per day.

Medications– Anti-emetic drugs (drugs that help in reducing vomiting) are prescribed. These can be administered in the form of shots, pills, suppositories or by intravenous route (through a vein in your arm). In some cases, steroids are administered intravenously.

IV fluids- In case of dehydration, vitamins, and electrolytes are usually administered intravenously along with normal saline.

Hyperemesis gravidarum cannot be prevented. However, the severity might reduce a bit by taking multivitamins before conceiving and by preventing unhealthy weight gain during pregnancy.

Maintain healthy pregnancy weight. Being overweight can increase your risk of having hyperemesis gravidarum.

Drink plenty of fluids in order to keep yourself from dehydration. You should drink slowly and use a straw to sip if possible.

Take vitamin supplements before and during pregnancy. Consult your doctor to know more about the required dosage for you.

Don't Consume larger and fewer meals. Divide your food into numerous small meals(11).

What is Helicobacter pylori : -

Helicobacter pylori (H. pylori) are common microaerophilic bacteria known to obstinately inhabit the human stomach mucous layer, affecting about half the world's population [12–14]. The pathogen is known to be present in the mucous, on the surface of the stomach lining and its presence causes chronic inflammation, which remains a major cause of prolonged gastritis. Also, H. pylori has been identified to increase the risk of developing gastric adenocarcinoma [15].

Apart from the gastrointestinal tract (GIT) related diseases such as gastroesophageal reflux disease, gastric ulcer and duodenal ulcer, infection from H. pylori has also been linked to some other diseases such as iron-deficiency anemia [16, 17], immune thrombocytopenia (ITP), [16, 18] cardiovascular diseases, [19, 20], hepatobiliary diseases [21, 22], diabetes mellitus [23], allergies, and asthma [24] among others.

There is no certainty in the mode of transmission for H. pylori infection; however, various epidemiological studies have made several claims in this regard. The primary means of spread of the disease has been linked to transmission from one individual to another and usually higher when occurring within a family [25–26]. The spread from person-to-person has been identified to be the most likely and could be by oral-oral, gastro-oral or fecal-oral [27]. In this regard, the practice of good hygiene and improved living conditions becomes an essential factor in reducing the rate of transmission of the infection [28].

The prevalence of infection from H. pylori varies geographically with the developing world carrying the higher burden [29].

Infection in peptic ulcer diseases (PUDs) patients ranges from almost 25% in countries of the industrialized world, and is anticipated to be around 90% in underdeveloped countries [30, 31]. The prevalence across countries in the West African region is generally high with variations existing from country to country. The reportedly high prevalence observed in Africa (79.1%) and Asia (54.7%) as compared to lower prevalence found in other geographic locations such as Northern America (37.1%) and Oceania (24.4%) [17] have been found not to correlate with the rather low occurrence of gastric cancer [32, 30]. This situation has been described as the “Asian and African enigmas”. These so-called “enigmas” have been explained by several factors including host genetic and immune response, different tumor-inducing potential of explicit strains of H. pylori as well as environmental factors [33, 34].

It is imperative to mention that an individual that is infected with H. pylori faces a strenuous task of getting rid of the bacterium and hence disease eradication, a situation that is largely attributed to the ever-increasing antibiotic resistance [35]. In the near future, the problems associated with H. pylori eradication are feared to increase looking at the current increasing infection rates and the gastroduodenal pathological outcomes. It is estimated that about 15% of infected individuals have an increased tendency of developing peptic ulcer [36], while a rate of 1–3% are found to have a bigger propensity of developing gastric malignancy in their lifetime [37, 38]. With the changing epidemiology of infection from this organism, the pattern of other related diseases also keeps changing.

. Influence of Host and H. pylori Genetic Factors on Infection: -

The distribution of H. pylori infection and the related pathology are mainly affected by host genetics and H. pylori virulence factors. In the progress of gastroduodenal diseases such as gastric cancer (GC), there seems to be an increase in the chances of development resulting from polymorphisms in several virulence genes. H. pylori genetic diversity is observed to be widespread and demonstrated in the disease outcome of various strains infection and pathogen interaction with their human host. Although not clearly described, the level of genetic multiplicity is considered as an element for adaptation of H. pylori in the stomach of the host and the clinical outcomes of

the infection [39]. A high through-put sequencing revealed the diverse nature of H. pylori genome, [40] and the bacteria genes, variability was adopted to establish a vibrant phylogeographic distinction, a marker for human migrations [41, 42]. Human genetic polymorphisms also compliment geographical distribution of H. pylori and the clinical consequences. For example, persons carrying genetic variation in the proinflammatory interleukin-1-beta (IL-1b) and IL-1 receptor adversary genes are two to three times more probable to develop GC [43]. Similarly, polymorphic tumor necrotic factor (TNF)-α as well as IL-16 genes were found to favor GC development during H. pylori infection [44, 45].

Environmental Factors in Helicobacter pylori Infection:-

Several factors have been reported to promote H. pylori infection and associated gastroduodenal diseases. Smoking, excessive alcohol intake, experience with high levels of carcinogens, and diet are proven to be significantly involved in the pathogenesis of gastroduodenal diseases including gastric cancer (GC) [46, 47]. Individuals with a higher intake of refined carbohydrates, pickled, salted, or smoked foods and dried fish and meat are at a higher risk of developing GC as compared to those who consume foods containing higher amounts of fiber, fresh vegetables, and fruits [48]. Antioxidant properties of micronutrients contained in foods with high amounts of fiber and fresh fruits and vegetables are capable of lowering the risk of GC development by exerting a positive effect on the mucosa of gastrointestinal tract.

gastroduodenal conditions by adversely affecting the mucosal protective mechanisms of the GI tract and also increasing the risk of H. pylori infection [49]. While the relation to the increase in infection may be due to antioxidant reduction or gastroduodenal immune system defense mechanism, the adverse effect on mucosal protective mechanisms can be attributed to an increase in the production of gastric acid coupled with a reduction in the production of bicarbonate [50].

Studies have shown that, smoking inhibits epithelial cell renewal resulting in the alteration of mucosal cell proliferation. This exposes the gastrointestinal tract to various aggressive factors leading to an improved likelihood of the induction of cell apoptosis during ulceration and ulcer healing [51, 52].

Pathogenesis of Infection and Clinical Outcomes: -

Besides environmental and genetic factors, there are other important characteristics of H. pylori such as the ability to enter, replicate, and persist in a host, which have been linked to the pathogenesis of gastroduodenal diseases [53 , 54]. These factors come into play after the individual is exposed to the organism. When H. pylori first enters the host stomach, it is faced with the task of surviving the hostile acidic condition of gastric acid bath where pH could be as low as 1.5. The organism utilizes its urease activity to break down urea into ammonium ions and carbondioxide. Once in the stomach, H. pylori reside on the epithelial surface. Movement into the mucosal lining is flagella-mediated, after which specific interactions between host cell receptors and bacterial adhesins follows. By these interactions, the bacterium latches onto the gastric epithelium and survives a possible displacement by the forces generated from the passing of food down the digestive tract.

H. pylori possess several strain specific virulent genes aside the typical virulence factors such as urease (UreA) and outer membrane protein (OMP) [55].

What are the symptoms of H. pylori infection?

Most people with H. pylori never have symptoms. But the bacteria can damage the inner protective lining of the stomach and cause other diseases, like a peptic ulcer. Symptoms of a peptic ulcer from H. pylori include:

dull or burning stomach pain (especially when you have an empty stomach), bloating, nausea, unexplained weight loss , vomiting,burping,and poor appetite.

While rare, stomach cancer is also an increased risk for people with H. pylori. Stomach cancer symptoms include:

Nausea and vomiting,dehydration ,poor appetite, poor appetite, unexplained weight loss, blood in the stool, feeling full early in a meal,, discomfort or swelling in the abdomen, stomach pain, fatigue or weakness.

Still, many of the symptoms of stomach cancer, peptic ulcers, and other diseases associated with H. pylori can be caused by other issues. If you experience any symptoms you're concerned about, talk with a doctor. You should also get medical attention right away if you experience:

trouble swallowing, anemia, blood in the stool, black-colored feces or vomit.

Diagnosis:-

Several tests and procedures are used to determine whether you have an H. pylori infection. Testing is important for detection of H. pylori but also to test after treatment to be sure it has been eliminated.

Stool tests. The most common stool test to detect H. pylori is called a stool antigen test that looks for foreign proteins (antigens) associated with H. pylori infection in your stool. Antibiotics, acid-suppressing drugs known as proton pump inhibitors (PPIs) and bismuth subsalicylate (Pepto-Bismol) can interfere with the accuracy of these tests. If you were previously diagnosed with and treated for H. pylori, your doctor will generally wait at least four weeks after you complete your antibiotic treatment to test your stool. If you are taking a PPI, your doctor will ask you to stop taking PPI medications for one or two weeks before the test.

A laboratory test called a stool polymerase chain reaction (PCR) test can detect H. pylori infection in your stool and mutations that may be resistant to antibiotics used to treat it. This test is more expensive and may not be available at all medical centers.

Breath test. During a breath test, you swallow a pill, liquid or pudding that contains tagged carbon molecules. If you have an H. pylori infection, carbon is released when the solution is broken down in your stomach.

Your body absorbs the carbon and expels it when you exhale. You exhale into a bag, and your doctor uses a special device to detect the carbon molecules.

As with stool tests, PPIs, bismuth subsalicylate (Pepto-Bismol) and antibiotics can interfere with the accuracy of this test. If you are taking a PPI, your doctor will ask you to stop taking the PPI medications for one or two weeks before the test. If you were previously diagnosed with and treated for H. pylori, your doctor will generally wait at least four weeks after you complete your antibiotic treatment to perform the breath test.

Scope test. You'll be sedated for this test, known as an upper endoscopy exam. This instrument allows your doctor to view any irregularities in your upper digestive tract and remove tissue samples (biopsy). These samples are analyzed for H. pylori infection.

This test is done to investigate symptoms that may be caused by other conditions such as gastric ulcer or gastritis that may be due to H. pylori.

This test isn't always recommended solely to diagnose an H. pylori infection because it's more invasive than a breath or stool test.

Treatment:-

H. pylori infections are usually treated with at least two different antibiotics at once, to help prevent the bacteria from developing a resistance to one particular antibiotic. also will prescribe or recommend an acid-suppressing drug, to help your stomach lining heal.

Drugs that can suppress acid include:

Proton pump inhibitors (PPIs). These drugs stop acid from being produced in the stomach. Some examples of PPIs are omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid) and pantoprazole (Protonix).

Histamine (H-2) blockers. These medications block a substance called histamine, which triggers acid production. One example is cimetidine (Tagamet HB).

Bismuth subsalicylate. More commonly known by the brand name Pepto-Bismol, this drug works by coating the ulcer and protecting it from stomach acid.

may recommend that you undergo testing for H. pylori at least four weeks after your treatment. If the tests show the treatment was unsuccessful, you may undergo another round of treatment with a different combination of antibiotic medications.

1.5 Objective

1.5.1 General objective

To investigate the relation between hyperemesis gravidarum and helicobacter pylori infection.

1.5.2 Specific Objective

1/ To search the infection by helicobacter pylori in pregnant women (Asyptomatic and with hyperemesis gravidarm).

2/ To detect H.pylori in non-pregnant women but with sign.

3/ To knw if sign different between pregnant and nonpregnant women.

4/ To record all clinical signs of pregnant women (symptomatic & Asymptomatic) and non-pregnant women.

Chapter 2

Methodology

2.1 Study Design

2.2 Study Setting

1) The Study for pregnant women will be conducted at :-

a) Khartoum Bahri Teaching Hospital. Located in Al-Danagla area, between Said Ali St. and Al-Ma Una St. west to Bahri Marketplace, Khartoum North, Sudan. It have various sections and clinics, and is split into two Departments; Basic Clinics & Emergency dept. and each one of them have Blood Banks, Medical Laboratories...etc

b) Omdurman Maternity Hospital.

2) The study for non-pregnant women will be conducted in both Hospitals for non - Pregnant women.

2.3 Study Population

Enrolled 100 pregnant women with Hyperemesis Gravidarum, and 50 non-pregnant women in cross-section.

2.3.1 Inclusion Criteria

100 Pregnant women during 1st trimester, or from 1st month till the 5th month. All of which are attendees in Bahri Teaching Hospital.

2.3.2 Exclusion Criteria

The pregnant and non-pregnant women whom choice is to refuse participating in the study.

2.4 Sample Size

The study sample will be calculated using sample size calculator.

[Total Number of study population = 150]

Confidence level = %

Margin of error = %

Population proportion = %

First year =

Second year =

Third year =

2.5 Sample Technique

Specific antigen for Helicobacter pylori will be detected in sample of the study group and will be compared with the non-pregnant group.

Determination of H. pylori Antigen in Stool specimen of pregnant women. The 1st trimester up to 5 months into pregnancy.

The presence of H. pylori antigens in stool specimens will be assessed using the rapid , one step H. pylori card test (on site H. pylori rapid test,Germany)Which is a chromatographic immunoassay used to diagnose H. pylori infection. On the test band region , monoclonal antibodies are used to pre-coat the membrane against H. pylori-antigens. Assessment involves allowing reacting between the sample and the colored conjugate (anti H. pylori monoclonal antibodies –red polystyrene micro-spheres) which has been per-applied to the test strip. Capillary action then pushes mixture (stool and puffer that included with the card in the test packet), up the membrane cause the colored particles to migrate. The capture of the colored conjugate by the specific antibodies of the membrane indicates appositive result. The mixture continues its passage across the membrane to the antibody that immobilized in the control band area. At this point, a red band emerges ,indicating an internal control for the reagent and confirmation of proper flow and adequate volume.

Participants stool sample will be tested following instructions from the test card manufacturer. Tests are demand negative if one red band appeared in the middle area in the region with the control line.

2.6 Data Management & Analysis

Data will be conducted & analyzed by ( ), and the outcomes will be presented in form of Tables & Pie Charts.

2.7 Ethical considerations & study

The tests & sample collection will be conducted after all the necessary consents & approvals are obtained from all the donators, in Bahri Teaching Hospital.

Chapter 3

Work Plan

3.1 Work of Plan (Pregnant Women)

Stages of Research	MONTH 1	MONTH 2	MONTH 3	MONTH 4	MONTH 5
Selection of topic					
Data collection					
Literature review					
Research methodology plan					
Research Technique					
Analysis and interpretation of data					
Findings & Recommendations					
Final research project					

3.2 Work of Plan (Non-pregnant women)

Stages of Research	During 5 Months
Selection of topic	
Data collection	
Literature review	
Research methodology plan	
Research Technique	
Analysis and interpretation of data	
Findings & Recommendations	
Final research project	

3.3 Time Plan

3.3.1 Collecting sample time

3.3.2 Analysis time

3.3.3 Result time

Excepted Result

Exposure to H. pylori appears to be associated with an increased risk of hyperemesis gravidarum. The residual heterogeneity might have different reasons. Given the high prevalence of H. pylori.

Heterogeneity also may be due to different methods of ascertaining exposure of H. pylori infection. Mainly serology tests were used and their positive and negative predictive values vary depending on the prevalence of H. pylori in the populations, which is known to vary from country to country and between subpopulations within the same country.

3.4 Budget

Items	Breakdown	Cost (SDG)
Preparation of the Questionnaire		
Data collection		
Transportation		
Data processing & analysis		
Reports writing & printing out		
Total		

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