INTRODUCTION

Nausea and vomiting are common problem during pregnancy with a frequency of 75% to 80% of pregnancies. It usually starts between first and second missed menstrual period and can continue up to 14-16 weeks of pregnancy. In some women nausea and vomiting are very severe and don't respond to simple diet manipulation and antiemetic agents. This culminates in dehydration, electrolytic imbalance and starvation ketosis and is called hyperemesis gravidarum (HG) ***(Kazemzadeh et al., 2014).***

Hyperemesis gravidarum is the most common indication for hospitalization in the first half of pregnancy and second only to preterm labor as the most common reason for hospital admission in pregnancy ***(Zhang et al., 2011).***

The condition is defined as uncontrolled vomiting requiring hospitalization, severe dehydration, electrolyte imbalance, ketonuria and weight loss of more than 5% of body weight ***(Wegrzyniak et al., 2012).***

The exact cause of HG is not well known and is probably multifactorial in which psychological factors, alteration of gastrointestinal motility, hormonal changes, infections, immunological, metabolic and anatomical factors appear to intervene ***(Verberg et al., 2005).***

The pathophysiology of Hyperemesis Gravidarum (HG) is still controversial. However, pregnancy may be associated with an increased susceptibility to Helicobacter pylori (H.P) infection and it has been hypothetically proposed that a shift in gastrointestinal tract pH during early pregnancy as a result of increased accumulation of woman's body fluid, steroid hormone changes, and immunologic tolerance, could lead the activation of latent H.pylori infection, which can exaggerate the symptoms of nausea and vomiting ***(Guven et al., 2011).***

H.pylori is a gram-negative flagellated spiral bacterium in the stomach. It has long been established that prolonged infection with this organism causes chronic gastritis, duodenal and gastric ulceration, and gastric cancer ***(Clark et al., 2012).***

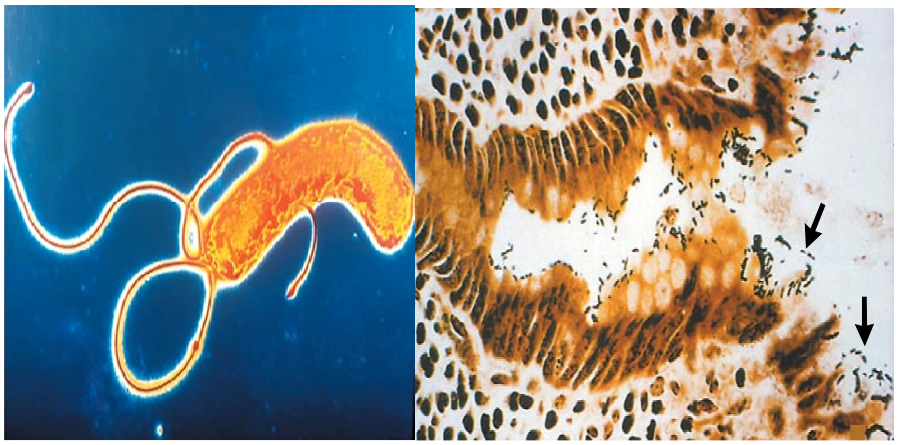

Figure (1) : Gastric-Biopsy Showing *H.P.* Adhering to Gastric Epithelium and Underlying Inflammation ***(Kenneth and McColl ,2010).***

H.pylori is transmitted through the following routes: person-to-person, oral-oral or fecal-oral and consumption of contaminated water and vertical transmission of H.pylori through breast feeding may also occur. Most individuals infected with H.pylori remain asymptomatic ***(Esquivel, 2013).***

H. pylori tests are divide into invasive and non-invasive. Invasive diagnostic methods using gastric tissue samples to detect H. pylori with culture, histopathology, polymerase chain reaction (PCR) and rapid urease test. Non- invasive tests are for detection of H. pylori antigen in stool and antibodies in serum, urine and oral samples. In addition, urea breath test (UBT) is based on the urease enzyme activity of H.P ***(Guarner et al., 2010)***

AIM OF THE WORK

To explore the association between Hyperemesis Gravidarum in pregnant women and Helicobacter pylori infection.

Study hypothesis:

In pregnant women with Hyperemesis Gravidarum, Helicobacter pylori may have a role in pathogenesis of this disease

Study question:

In pregnant women with Hyperemesis gravidarum, does Helicobacter pylori play a role in the pathogenesis of this disease?

Chapter (1)

PHYSIOLOGICAL CHANGES WITH PREGNANCY

Pregnant women undergo several adaptations in many organ systems. Some adaptations are secondary to hormonal changes in pregnancy, while others occur to support the gravid woman and her developing fetus. Some of the changes in maternal physiology during pregnancy include, for example, increased maternal fat and total body water, decreased plasma protein concentrations, especially albumin, increased maternal blood volume, cardiac output, and blood flow to the kidneys and uteroplacental unit, and decreased blood pressure . The maternal blood volume expansion occurs at a larger proportion than the increase in red blood cell mass, which results in physiologic anemia and hemodilution. Other physiologic changes include increased tidal volume, partially compensated respiratory alkalosis ***(Costantine, 2014).***

Endocinal system:

Majority of endocrine changes in pregnancies is due to the increase in activity in the pituitary, thyroid and adrenal glands in addition to placental hormones released from the fetoplacental unit. Duration of pregnancy, protein hormones

such as human chorionic gonadotropin (hCG), human somato-mammoprote's, human chorionic thyrotropin released and also progesterone and estrogen are released from the placenta at different levels . These hormones, primary or secondary, is thought to be responsible for many physiological changes in the skin developed during pregnancy ***(Akkoca et al.,2014)***

Hematologic and coagulation system:

White (WBC) and red blood cell (RBC) counts increase during pregnancy. The first is thought to be secondary to bone marrow granulopoiesis; whereas the 30% increase in RBC mass (250–450 mL) is mainly driven by the increase in erythropoietin production. The higher WBC count can sometimes make diagnosis of infection challenging; however normally the increase in WBC is not associated with significant increase in bands or other immature WBC forms ***(Pacheco et al., 2013).***

Placental lactogen may enhance the effect of erythropoietin on erythropoiesis. Maternal erythropoietin production is enhanced in normal pregnancy and when red cell hemoglobin content is lower and subclinical iron deficiency exists ***(Ervasti et.al,2008).***

A greater expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume is

responsible for the fall in hemoglobin levels (i.e., physiological or dilutional anemia of pregnancy) observed in healthy pregnant women. The greatest disproportion between the rates at which plasma and erythrocytes are added to the maternal circulation occurs during the late second to early third trimester. (Lowest hematocrit is typically measured at 28–36 weeks ***(Whittaker et.al 1996).***

Pregnancy is a hypercoagulable state secondary to blood stasis as well as changes in the coagulation and fibrinolytic pathway such as increased plasma levels of clotting factors (VII,VIII,IX,X,XII), fibrinogen, and von Willebrand factor. Fibrinogen increases starting in the first trimester and peaks during the third trimester in anticipation of delivery. Prothrombin and factor V levels remain the same during pregnancy. Whereas, protein S decreases in pregnancy, protein-C does not usually change and thus can be assayed if needed in pregnancy. Free antigen levels of the protein S above 30% in the second trimester and 24% in the third trimester are considered normal during pregnancy ***(Pacheco et al., 2013).***

Cardio-vascular system:

Pregnancy is associated with significant anatomic and physiologic remodeling of the cardiovascular system. Ventricular wall mass, myocardial contractility, and cardiac compliance increase ***(Rubler et al., 1977).***

Both heart rate and stroke volume increase in pregnancy leading to a 30–50% increase in maternal cardiac output ***(Clark et al., 1989).***

Respiratory system:

Pregnancy is associated with increase in tidal volume by 30–50%, which starts early in the first trimester. While the respiratory rate is not different compared to non-pregnant state, minute ventilation (the product of respiratory rate and tidal volume) is significantly increased, similarly, by 30–50%. These changes are mainly driven by the increase in progesterone concentrations in pregnancy **(*McAuliffe et al., 2002)*.**

Renal system:

The effects of progesterone and relaxin on smooth muscles are also seen in the urinary system leading to dilation of the urinary collecting system with consequent urinary stasis, predisposing pregnant women to urinary tract infections ***(Rasmussen and Nielse, 1988).***

This is more common on the right side secondary to dextrorotation of the pregnant uterus, and the right ovarian vein that crosses over the right ureter. Both renal blood flow and glomerular filtration rate (GFR) increase by 50%, as early as 14 weeks of pregnancy ***(Davison and Dunlop, 1984).***

Gastro-intestinal system:

Pregnancy causes physiologic changes in the gastrointestinal (GI) tract which result in patient complaints of nausea, emesis, constipation and gastro-esophageal reflux ***(Longo et al., 2010).***

Appetite:

During pregnancy, the women's appetite and food intake fluctuate. Early in pregnancy , some women have nausea with or without vomiting (morning sickness) , possibly in response to increasing levels of human chorionic gonadotrophin (HCG) and altered carbohydrates metabolism ***(Gordon,2002).***

Women also may have changes in their sense of taste, leading to cravings and changes in dietary intake. Some women have non food cravings (called pica) such as ice, clay and laundry starch ***(Gordon, 2002).***

Mouth :

The gums become hyperemic, spongy and swollen during pregnancy. They tend to bleed easily because the increasing levels of estrogen cause selective increased vascularity and connective tissue proliferation (a non specific

gingivitis). Some pregnant women complain of ptyalism (excessive salivation) which may be caused by stimulation of salivary glands by eating starch ***(Cunningham et al., 2005).***

Esophagous and stomach:

Physiological changes to the gastrointestinal system in pregnancy may have a role in the development of nausea and vomiting. Generalized relaxation of smooth muscle is mediated by progesterone and culminates in reduced oesophageal pressure and delayed gastric emptying ***(Mansour and Nashaat, 2010).***

Increased estrogen production causes decreased secretions of hydrochloric acids; therefore peptic ulcer formation or flare – up of existing peptic ulcers is uncommon during pregnancy and may improve ***(Winbery and Blaho, 2001).***

Herniation of the upper portion of the stomach (hiatal hernia) occurs after the seventh or eighth month of pregnancy in about 15 % to 20% of pregnant women. This condition results from upward displacement of the stomach, which causes the hiatus of the diaphragm to widen ***(Winbery and Blaho, 2001).***

Small intestine:

In pregnancy, the rise in progesterone leads to delayed gastric emptying and prolonged small bowel transit time, by ~30–50%. Increased gastric pressure, caused by delayed emptying as well as compression from the gravid uterus, along with reduced resting muscle tone of the lower esophageal sphincter, sets the stage for gastro-esophageal reflux during pregnancy ***(Cappell and Garcia, 1998).***

Large intestine :

Many changes that pregnancy exerts on the colon lead to increased symptoms of constipation. The colon may be subject to the same decreases in motility that affect the other portions of the gastrointestinal tract. Progesterone has been shown to alter colonic transit time in rats ***(Chen et.al ;1995).***

The functional changes that occur with the enlarging uterus may mechanically limit colonic emptying and probably is the main reason for symptomatic constipation in late term. There is also a significant increase in water and sodium absorption secondary to the increased aldosterone levels during pregnancy, leading to reduced stool volume and prolonged colonic transit time ***(Everson ,1992).***

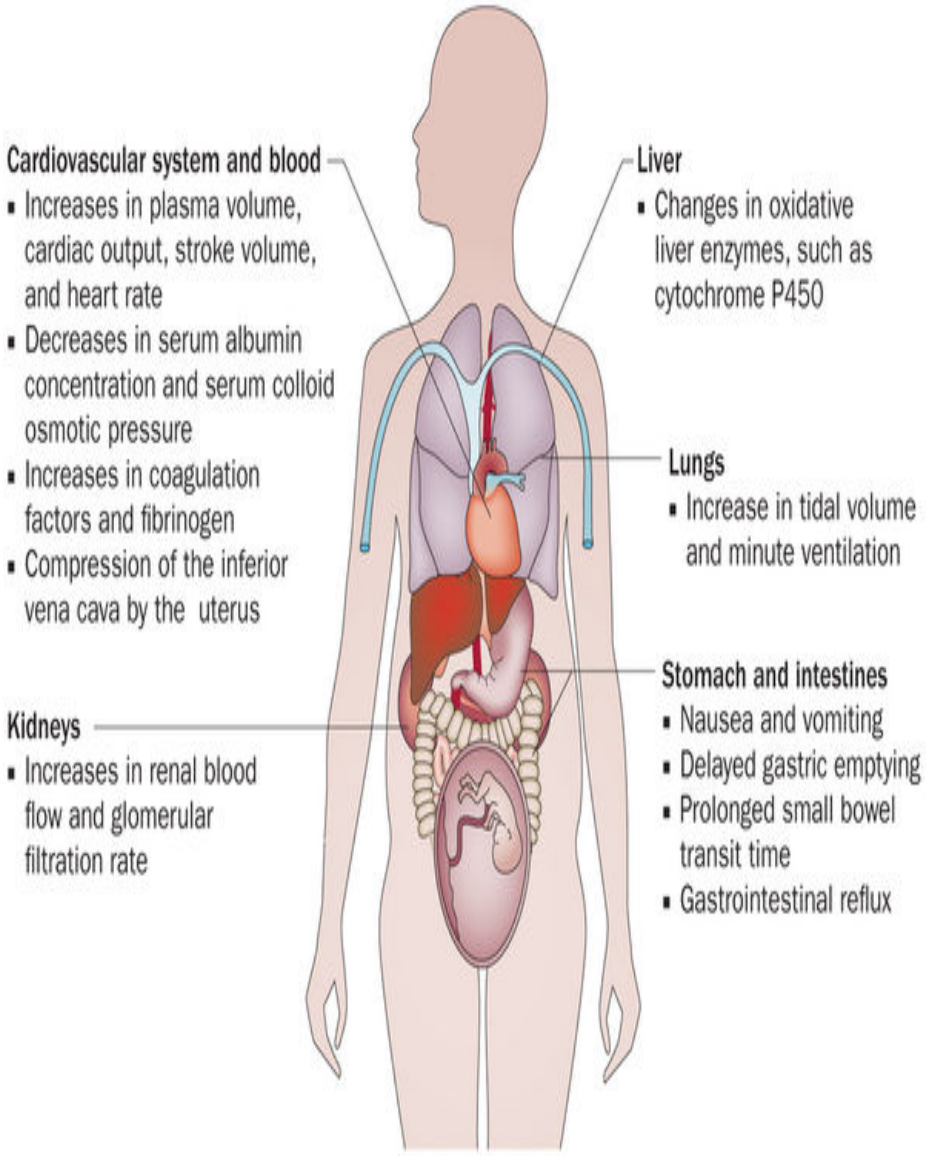

Figure (2): Physiological changes in pregnancy that alter drug pharmacokinetics ***(Pieper ,2015).***

Chapter (2)

EMESIS & HYPEREMESIS GRAVIDARUM

Nausea and vomiting of pregnancy (NVP) occur in 50–90% of pregnancies, with nausea and vomiting in approximately 50–55% and nausea alone in 25% . Although NVP has been commonly referred to as "morning sickness," nausea can occur at any time of the day. The usual onset for NVP is between 4–9 weeks gestational age with maximal symptoms at 12–15 weeks and resolution by 20 weeks gestational age ***(Clark et al., 2012).***

Symptoms including nausea, gagging, retching and vomiting may persist 'round the clock despite the common term morning sickness ***(Clark et al., 2014).***

A smaller number of pregnant women (approximately 0.3–1%) have a more severe form of nausea and vomiting – hyperemesis gravidarum which is characterised by persistent vomiting, weight loss of more than 5%, ketouria, electrolyte abnormalities (hypokalaemia) and dehydration ***(O'Carroll et al., 2011).***

Younger primigravida women with less education also are at higher risk. Certain obstetric conditions such as multiple gestation, trophoblastic disease and fetal anomalies (trisomy 21 & hydrops fetalis) are associated with an increased risk of hyperemesis gravidarum ***(Lee and Saha, 2011).***

Etiology:

Although the pathophysiology for HG is not clear, many hypotheses have been proposed to explain the etiology and pathophysiology of HG including psychological factors, gastrointestinal tract dysfunction, endocrinologic changes, infections, immunological and metabolic causes and anatomical factors. However, there is no single theory to provide an adequate explanation for all the manifestations of HG ***(Niebyl, 2010).***

A) Endocrine Theories:

Human chorionic gonadotrophin (HCG)

HCG is the most likely endocrine factor which accounts for the development of HG. This conclusion is based on observed associations between increased production of HCG (as in molar or in multiple pregnancies) and the fact that the incidence of hyperemesis is highest at the time when HCG production reaches its peak during pregnancy (around 9 weeks gestation) However, there is no evidence to support this hypothesis and some pregnant women do not experience nausea and vomiting despite elevated HCG-levels ***(Jueckstock et al., 2010).***

Hyperthyroidism

Thyroid function is physiologically altered during pregnancy including stimulation by HCG. Hyperthyroidism with normal fT3 and fT4 levels but decreased levels of thyroid

stimulating hormone (TSH), may also be implicated in HG. A self-limiting, transient hyperthyroidism of hyperemesis gravidarum has been proposed according to the findings of a screening series in 1900 pregnant women who showed markedly increased HCG and fT4 levels ***(Jueckstock et al., 2010)***

B) Psychological:

Nausea and vomiting in pregnancy have been correlated with poor communication between the woman and her partner, home life stressors, and insufficient information about the pregnancy,but it is difficult to prove causality. Nausea and vomiting in pregnancy itself may lead to considerable psychosocial stress through altered family, social, and occupational functioning ***(Tan et al., 2010).***

There may also be significant psychosocial morbidity associated with hyperemesis. Multiple studies have demonstrated an association with decreased psychosocial well being, depression and anxiety ***(Munch et al., 2011).***

C) Gastro-Intestinal Tract Dysfunction:

Physiological changes to the gastrointestinal system in pregnancy may have a role in the development of nausea and vomiting. Generalised relaxation of smooth muscle is mediated by