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PREGNANCY, PEPTIC ULCER AND GERD: A TIME SERIES OF CORRELATION

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ABSTRACT

Background/ introduction: It is widely agreed that 1. During pregnancy, incidence/ prevalence of peptic ulcer/ erosion at esophagus/ stomach/ duodenum as well as H pylori infection is minimal 2. Relapse may occur by the term end. But past studies are not in the same cohort (same ladies are not followed with and without pregnancy) **Objectives**: to study the effect of pregnancy on incidence/ prevalence of peptic ulcer/ erosion at esophagus/ stomach/ duodenum as well as H pylori infection in the same cohort of ladies. **Materials and methods** : 11 ladies known for chronic peptic ulcer during non-pregnant state were followed throughout pregnancy for estimates of pathology. Endoscopy (for ulceration/ erosion) and breath urease test (for H pylori; supportive by fecal Hp antibody verification) were used at baseline (pre-pregnant), and 4 times during pregnancy (2, 4, 6, 8 months). **Statistics**: Normaquant and PPCC (for testing normality of data), IBM SPSS Statistics 22.0 - August 2013 (for Spearman's rank correlation), Excel (MS window 2008) for graph. **Results** : Spearman's test result : r=-0.0086 df=1022 z=-0.2741 p=0.3920; Significant reduction of incidence/ prevalence of peptic ulcer/ erosion at esophagus/ stomach/ duodenum as well as H pylori infection was seen during pregnancy but relapse/ rise was seen towards term end.

Discussion and conclusion: Pregnant ladies known to have GIT erosive pathologies require maximal concern around Puerperium.

KEYWORDS : peptic ulcer, H. pylori, pregnancy, endoscopy, breath urease test, time-series analysis.

INTRODUCTION

Up to 85% of all pregnant women experience some form of nausea and vomiting during their pregnancy. [1] Nausea and vomiting during pregnancy, typically occur between the fourth and the 10th week of gestation, with resolution by 20 weeks of gestation. [2] The endocrine factor most commonly invoked is human chorionic gonadotropin hormone (HCG) on the basis of the observed temporal association, i.e. incidence of hyperemesis is highest at the time that HCG production reaches its peak. In addition, hyperemesis is said to have a higher incidence in the conditions associated with elevated HCG concentrations such as twin and molar pregnancies. [1] One study found that women hospitalized for hyperemesis had a 50% increased chance of having a female fetus compared to controls. The usual explanation for this may be higher oestrogen concentrations. [3] When limited to the gastrointestinal tract, gastric dysrhythmias — acute losses of the normal gastric slow wave frequency of three cycles per minute — are related to stomach dysfunction and nausea in pregnancy. [4]

There is a widespread and age old [4,5] assumption in medical community that due to progesterone mediated slowing of peristalsis, there are least chances of peptic ulcer during pregnancy. 88% of women with known peptic ulcer disease prior to gestation experience amelioration of symptoms during pregnancy. [6] But exacerbation of peptic ulcer symptoms might occur in the last trimester of pregnancy and the early postpartum period, and results in significant morbidity and mortality to mother and fetus[4] Sometimes, slowing of peristalsis has been ascribed the credit of diminished peptic ulcer [7] but increased histaminases can be a more valid reason [8] But atropine has been expectedly and already shown to slow gastric emptying and increase GERD (gastroesophageal reflux disease) [9] might increase the cases of erosion and even ulceration in esophagus. Actually higher gastric acid secretion instead of the disorders of esophageal motility is closely related to the GER/RE accompanied with DU patients. [10] A small number of reports of perforation and hemorrhage from peptic ulcer in pregnant women resulting in maternal and fetal mortality have been published so far. [11] The majorities of these instances were unrecognized during life and were necropsy findings.

And pregnancy has long been acknowledged as a condition that predisposes to GERD and heartburn as the predominant symptom is estimated to occur with a frequency of 30% to 50% in pregnant women. [12] Most pregnant women, in fact > 85%, show symptoms like nausea and vomiting and this can hide a GERD. [4] Upper gastrointestinal endoscopy is the procedure of choice to evaluate intractable reflux symptoms or complications. [13]

The urea breath test is based on the ingestion of carbon-labeled urea, which is hydrolyzed by H pylori urease to labeled bicarbonate and exhaled as labeled carbon dioxide, which can be measured. This test is quick, inexpensive, and highly accurate—the ideal test for the presence and eradication of H pylori [14] Antacids or sucralfate are considered the first-line drug therapy. If symptoms persist, any of the H_2-receptor antagonists can be used. Proton pump inhibitors are reserved for women with intractable symptoms or complicated reflux disease. [12] A decade ago, this concern seemed more insidious seeing the opposite trend of H. pylori infection and GERD i.e. eradication of H. pylori infection increases incidences of GERD. [15, 16] It's notable that the predicted rank order for the presence of GERD and its complications (peptic stricture, Barrett's esophagus, and adenocarcinoma of the gastric cardia) is highest in the population without *H. pylori* infection, less in those with *H. pylori* infection, and least in those infected with *cagA*-positive *H. pylori*. [17] But this concern was denied later on [18] and a simultaneous improvement in H.pylori induced duodenal ulcer and GERD was noted [19] and H. pylori was shown to have no protective role against GERD. [20]

Actually Multiple strains of H. pylori are involved and those possessing the vacAs1 genotype and/or cagAare associated with peptic ulcer. GERD patients, infected with H. pylori mostly carry less virulent strains possessing neither cagAnor iceA1. A research established that virulent strains protect against the development of GERD. [21] Moreover, virtually every trial comparing the PPB against H2RA has been done in patients with erosive esophagitis. This is understandable, for healing of the breached mucosa is clearly recognizable and healing rates, therefore, measurable. [22] In patients with symptomatic GERD but with normal mucosa, however, symptom improvement is the only quantifiable parameter, and being subjective is less accurate. Yet in reflux disease about half the patients investigated in hospital have normal endoscopy and the proportion in general practice is higher still. [23, 24] In a very old study[25] , compared to normal subjects, patients with gastric ulcer had significantly higher concentrations of bile acids than normal subjects, both before and after the meal. But later on, this finding too was denied.[26] Now it has been established that neither H. pylori

infection nor H. pylori eradication causes gastroesophageal reflux disease (GERD). H. pylori eradication also does not impede anti-secretory drug therapy of GERD.[27] Thus misunderstandings of the negative association between H. pylori infection and GERD and/or Barrett's esophagus and misuse of the epidemiologic concept of "protection" led to considerable confusion and likely resulted in some patients receiving poor care. [27] Actually, antral gastritis (predominant) due to *H. pylori* infection causes hypergastrinemia and greater parietal cell mass (with higher values of acid output) and is the cause of duodenal ulcer – a disease of the 20th century. [28]

In contrast, the absence of *H. pylori* in the gastric mucosa with improved sanitation, results in increased acid output in the stomach (in the absence of corpus gastritis), precipitating peptic esophageal ulcer - a disease of the 21st century. [28] This paradigm shift of ulceration from the duodenum to the esophagus, observed recently in developed countries, results from the differences of *H. pylori* prevalence in the gastric mucosa of the population, in relation to time. Such a shift is likely to extend to developing countries in the 21st century. [28] Seeing this shift and increased incidence of GERD in pregnancy, this study was planned with the objective of assessing the change in GERD/ Peptic ulcer status throughout pregnancy in a previously (pre-pregnancy) known ulcer patient.

MATERIALS AND METHODS

Inclusion criteria

1. Chronic female patients of peptic ulcer who conceive and maintain pregnancy
2. Adult Patient compliant and consenting to the endoscopy and urea breath test

Exclusion criteria

1. Patient with complicated pregnancy
2. Patient with other chronic disease/ disability
3. Patients on antibiotics/ ulcerogenic drug for any reason
4. Non-adult pregnancies, even if chronic cases of peptic ulcer, were excluded

Method

After due ethical clearance and consent, 11 patients were enrolled. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, ICH/Good Clinical Practice[29] and good clinical practice regulatory requirements in India. [30]

A prospective time series of peptic ulcer/ erosion is noted in esophagus, gastric cavity and duodenum at the baseline (without pregnancy). If more than one data of pre-pregnancy ulceration was available, an arithmetic mean was taken. Due to chances of zero ulceration, geometric mean was not suitable.

All the outpatients were aged between 18 and 35 years, with duodenal or gastric ulcer diagnosed by upper digestive system endoscopy in the A, H or S phases, according to the Sakita classification criteria [31] and correlated to Sakita Miwa classification. [32] The diagnosis of functional dyspepsia was based on Rome II criteria. [33]

Endoscopy

Endoscopic observations were scored using the following definitions. Petechiae were submucosal hemorrhages having no mucosal break. Erosions were definite mucosal discontinuities, without depth. Ulcers were mucosal breaks ≥ 3 mm in length with unequivocal depth.

All lesions characterized as ulcers were assessed by video review of the mucosal lesion with the endoscope placed tangentially to the lesion and with unequivocal depth confirmed through video review of the lesion by an adjudication committee of experienced blinded gastroenterologists. Measurement of lesion size was aided by a 6 mm extended biopsy forceps placed adjacent to lesions.

A modified Lanza scoring system was used to assess mucosal injury as follows: Grade 0, no injury; Grade 1, 1 – 10 petechiae; Grade 2, > 10 petechiae or 1 – 5 erosions; Grade 3, 6 – 10 erosions; Grade 4, > 10 erosions and / or an ulcer. A gastro-duodenal composite score was derived by adding the scores for the stomach and duodenum. [34]

Patients underwent esophagogastroduodenoscopy without iv sedation using only lidocaine spray.

Helicobacter pylori

The 13C test requires an initial expense of buying a mass spectrophotometer but, because it is not radioactive, has the additional advantage that it can be used with children and pregnant females. It has a sensitivity of 95% and specificity of 96%. [35]

Radioactive counterpart using 14C with nearly same sensitivity and specificity has not been found so safe during pregnancy and requires scintillation counter instead of simple colorimeter used in the 13C using apparatus – hence avoided. [35]

Thus main diagnosis of presence of H. Pylori was done by Hp breath test. Following endoscopy, each patient underwent the urea breath test (UBT) by carbon 13 using a Isomax 2000 device; results greater than 5 (cut-off value) were considered positive. [36]

Hp fecal antigen (Premier H. Pylori, Meridian Diagnostic Inc.) tests was carried out for confirmation (seeing pregnancy, histological test based on biopsy was avoided). Polyclonal antibody tests used on stool specimens showed a sensitivity of 93% and specificity of 93%. [35]

Statistics

As the sample size is small (11) and normality of distribution is excluded by Normaquant as well as PPCC (probability plot correlation co-efficient) – seeing ordinal nature of the ulcer grading data, Spearman's rank correlation test was used for analysis of significant change. [37] For statistical calculation of Spearman's correlation coefficient, IBM SPSS Statistics 22.0 - August 2013 version has been used.

RESULTS

Table 1 : Rome II symptom score

Patient no	Baseline	2nd month	4th month	6th month	8th month
1	29.5 ± 5.4	18.6 ± 5.8	13.3 ± 3.6	13.4 ± 3.9	18.8 ± 5.9
2	28.7 ± 3.9	18.1 ± 4.3	13.1 ± 4.4	13.0 ± 3.7	18.7 ± 4.3
3	29.0 ± 4.2	19.2 ± 3.6	14.2 ± 3.7	14.2 ± 3.4	20.2 ± 3.1
4	26.6 ± 6.6	17.5 ± 5.6	12.9 ± 4.2	13.1 ± 4.0	18.5 ± 4.9
5	24.9 ± 4.3	15.8 ± 4.5	13.1 ± 4.6	13.3 ± 4.2	17.8 ± 4.3
6	27.7 ± 4.1	16.7 ± 4.7	13.4 ± 5.1	13.2 ± 3.8	16.6 ± 4.4
7	25.3 ± 5.4	15.8 ± 3.9	12.8 ± 3.6	12.9 ± 3.6	15.7 ± 3.3
8	33.8 ± 3.1	19.2 ± 2.1	15.6 ± 4.8	15.9 ± 5.1	19.8 ± 2.7
9	29.5 ± 4.8	18.1 ± 3.4	14.4 ± 3.8	14.3 ± 4.2	18.0 ± 3.6
10	27.5 ± 4.6	17.4 ± 5.1	13.5 ± 3.9	13.1 ± 4.6	17.7 ± 5.5
11	35.4 ± 4.2	20.1 ± 3.6	14.6 ± 4.3	15.1 ± 4.1	20.7 ± 3.7
*P < 0.05 in all the calculations					

Spearman's test result : r=-0.0086 df=1022 z=-0.2741 p=0.3920

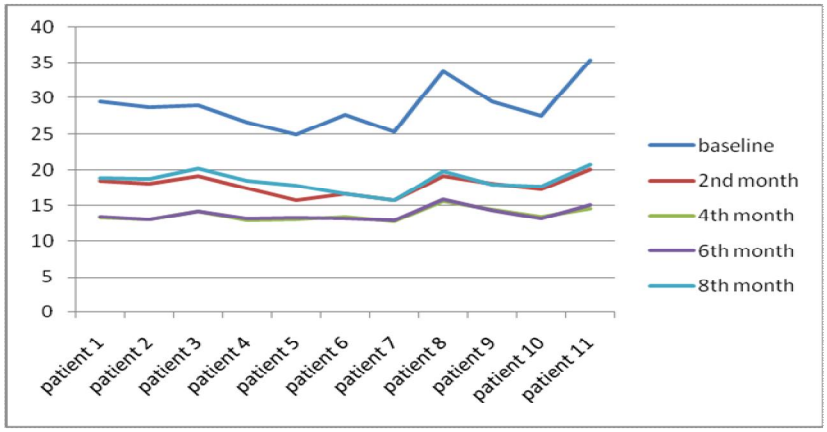

Figure 1: Rome II symptom score

Table 2 : Breath urease test (for H. pylori)					
Patient no	baseline	2nd month	4th month	6th month	8th month
1	+	–	–	–	–
2	–	–	–	–	–
3	+	–	–	–	–
4	–	–	–	–	–
5	–	–	–	–	–
6	–	–	–	–	–
7	–	–	–	–	–
8	+	+	–	–	+
9	+	–	–	–	+
10	–	–	–	–	–
11	+	+	+	–	+

Table 3 : Endoscopy test (ulcer count - esophageal/ gastric/ duodenal*)					
Patient no	baseline	2nd month	4th month	6th month	8th month
1	$E_2G_8D_0$	$E_0G_1D_0$	$E_0G_0D_0$	$E_0G_0D_0$	$E_0G_2D_0$
2	$E_0G_{11}D_0$	$E_0G_2D_0$	$E_0G_0D_0$	$E_1G_0D_0$	$E_0G_2D_0$
3	$E_1G_{16}D_0$	$E_0G_3D_0$	$E_0G_1D_0$	$E_0G_1D_0$	$E_0G_3D_0$
4	$E_3G_7D_0$	$E_0G_0D_0$	$E_0G_0D_0$	$E_0G_0D_0$	$E_0G_1D_0$
5	$E_0G_5D_0$	$E_0G_1D_0$	$E_0G_0D_0$	$E_0G_0D_0$	$E_0G_1D_0$
6	$E_0G_0D_8$	$E_0G_0D_1$	$E_0G_0D_0$	$E_1G_0D_0$	$E_0G_0D_2$
7	$E_3G_5D_0$	$E_1G_0D_0$	$E_0G_0D_0$	$E_1G_2D_0$	$E_1G_3D_0$
8	$E_5G_{19}D_0$	$E_2G_4D_0$	$E_1G_0D_0$	$E_1G_2D_0$	$E_2G_4D_0$
9	$E_7G_8D_0$	$E_3G_0D_0$	$E_1G_0D_0$	$E_1G_0D_0$	$E_2G_3D_0$
10	$E_0G_8D_0$	$E_0G_0D_0$	$E_0G_0D_0$	$E_0G_0D_0$	$E_0G_1D_0$
11	$E_0G_0D_{21}$	$E_0G_0D_5$	$E_1G_1D_0$	$E_0G_0D_0$	$E_0G_0D_4$
* e.g. baseline value of ulceration/ erosion in the first patient was 2 in esophagus, 8 in gastric cavity and 0 in duodenum					

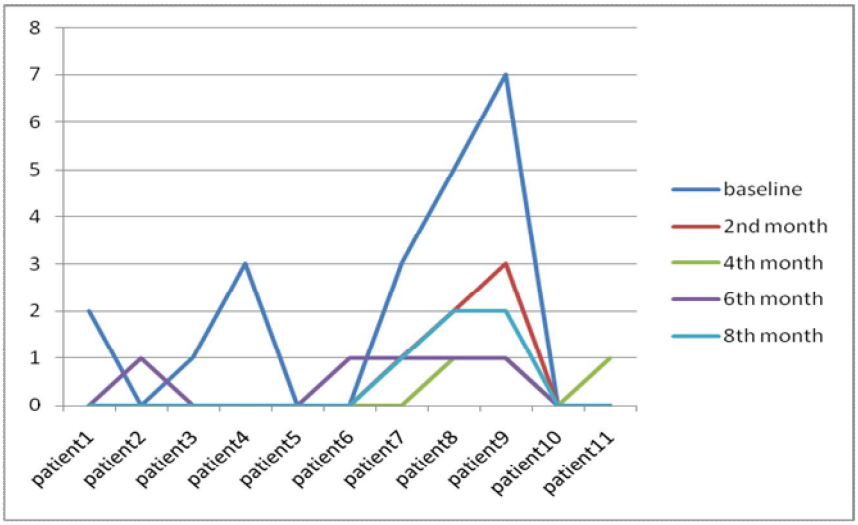

Figure 2 : Esophageal erosion through pregnancy

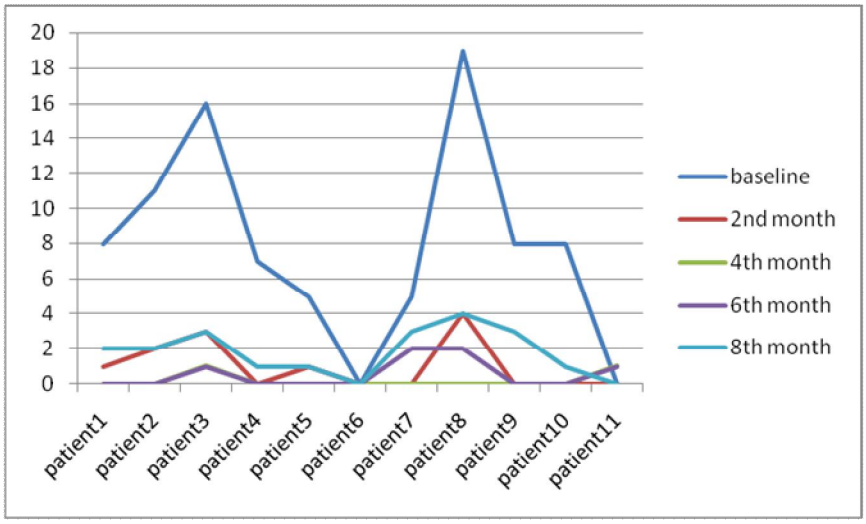

Figure 3: Gastric ulceration through pregnancy

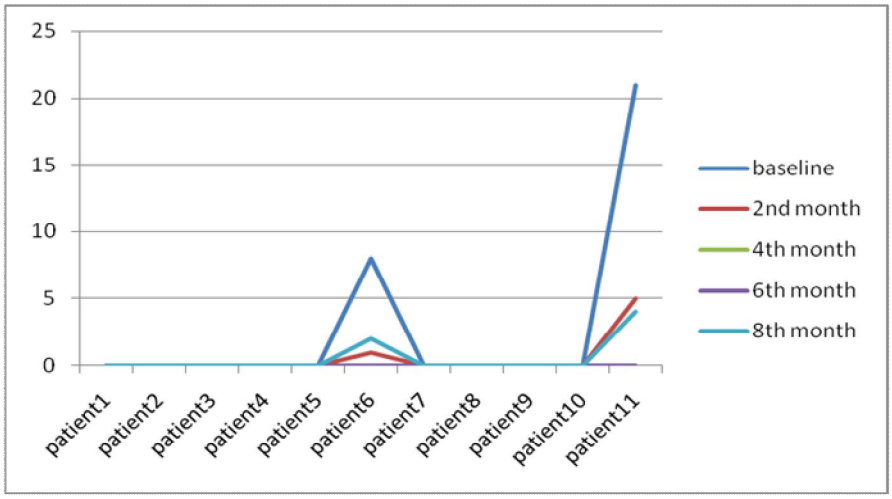

Figure 4: Duodenal ulceration through pregnancy

DISCUSSION

Till date most data were collected separately on non-pregnant females and pregnant ones [Bardhan, 1996] – same cohort of chronic ulcer patients followed during pregnancy is not involved in any study to the best of author's knowledge. This study has tried to fill the gap with the study.

As the result shows, and in accordance with many new and old researches [James, 1948] [Grosfeld et al, 1968] [Malfertheiner et al, 2009], there is significant reduction of erosion/ ulceration after conception – but it has not been totally curative, especially in serious cases. H. pylori population also dwindled down and didn't rise till the pregnancy continued (measured up to 8th month) as shown in other studies too [Malfertheiner et al, 2009].

The first trimester prevalence of the lesser pathology is mostly shadowed by nausea and vomiting sensation which is taken to be inherent to pregnancy by doctors as well as patients. Otherwise conception is not eradicative to all erosive pathologies of GIT as mostly taken as a thumb rule.

Moreover, second trimester (4th and 6th month of pregnancy) is the period of minimal erosive pathology as seen clearly in figures 1-4 and tables 1-3 – difference of incidence of erosive pathology in these two measurements is insignificant (pathology of 2nd and 8th months correspond while that of 4th and 6th month nearly coincide as explained by results of Spearman's rank correlation).

In the last trimester (8th month of pregnancy) there is a recurrence of pathology incidence nearly reaching the level of 2nd month. This is especially dangerous if overlooked in puerperium and otherwise known cases of serious and chronic ulceration.

CONCLUSION

Though expectedly occurrence of ulceration and/or erosion in esophageal, gastric and duodenal sites are less in the same female patient of chronic pathology when she conceives but relapse are commoner at term end and it should not be overlooked.

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