Association of Heartburn During Pregnancy With the Risk of Gastroesophageal Reflux Disease

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Background & Aims: **Heartburn and gastroesophageal reflux disease (GERD) during pregnancy are accepted as an innocent condition. The effect of heartburn during pregnancy on the initiation or progress of GERD is not known. We aimed to determine the predisposition effect of heartburn during pregnancy for presenting with GERD in the future.** ***Methods:*** **A validated reflux questionnaire was applied to 1180 randomly selected women aged between 18–49 years who had given birth to at least one delivery. Frequent symptoms were defined as a major symptom (heartburn and/or regurgitation) occurring at least once a week or more. Occasional symptoms were defined as an episode of one of the major symptoms occurring less than once a week within the past 12 months.** ***Results:*** **The mean live delivery rate was 2 ± 1 (range, 1–10). The prevalence of GERD was 7.4%. Whereas the prevalence of GERD for women with a history of just 1 delivery was 1.5%, more than 2 deliveries were accompanied with risk of 15.1% ($P < .001$). In the group with no heartburn during pregnancy only 5.5% had GERD ($P < .00001$). If there was heartburn during any of the pregnancies, the risk was 17.7%; and more than 2 pregnancies with a history of heartburn accompanied 36.1% risk of having GERD. Logistic regression analysis showed that the risk is independent from obesity and age.** ***Conclusions:*** **The risk of GERD is increased by the presence of heartburn during pregnancy. This association is independent of obesity and age. Heartburn during pregnancy might not be accepted as an innocent and temporary condition.**

Heartburn and gastroesophageal reflux disease (GERD) are common during pregnancy.[1–3] The prevalence reaches up to 50% in general. It has been published that 25% of pregnant women have had heartburn everyday.[4] Bainbridge et al[2] suggested that symptoms were increased in multiparous women compared with primiparous women, and whenever heartburn was present during the first pregnancy, it was likely to recur during subsequent pregnancies. Heartburn during pregnancy is generally accompanied by normal endoscopic findings. No data have been published about the GERD-related additional symptoms; however, there is a general belief that these symptoms are not common.[5] For all of these reasons heartburn and moreover GERD during pregnancy are accepted as an innocent condition. Clinical observations support this opinion that heartburn disappears almost immediately after labor. However, none of the studies addressed the question whether GERD during pregnancy disappears completely without any predisposing effect for having GERD in the future; in other words, whether the presence of heartburn during pregnancy makes the esophagus of a woman more vulnerable to GERD than a woman who has not experienced significant heartburn during pregnancy.

We performed a study evaluating the GERD-related major symptoms (heartburn, acid regurgitation) during pregnancy and existence of current symptoms. The aim of the study was to evaluate the predisposing effect of heartburn during pregnancy on the presence and severity of post-pregnancy GERD. Turkey and the Bornova area are particularly suitable for this study because the number of deliveries is high (up to 10 per woman), and the prevalence of GERD in the population is very similar to Western countries (20%).[6]

Methods

The study was performed in the Bornova district, which is a part of the third largest city, Izmir, Turkey. The population of Bornova is 400,000. Twenty-two primary health care units (3 also have maternal and pediatric care units) that are run by the Ministry of Health have records of the population. The subpopulation of women between ages 18–49 years was 122,000. The subtarget population of women 18–49 years old who had undergone labor more than 1 year ago was 80,000. On the basis of the goal of achieving a 99% confidence interval with 3% acceptable worst and 20% prevalence, sample size was calculated to be approximately 1200. According to the population size of each primary health care unit, a proportional sampling was planned. By using the records of the inhabitants in the area of the unit, an age-stratified random sampling was performed. Subjects were excluded if they died or moved from the city before the interview, were currently pregnant, possessed any mental or psychiatric disease, were unable to communicate as a result of dementia, refused to attend the survey, or had an incorrect address or name within the registration system. Interviewers attempted to find each selected subject on 3 visits on 3 nonconsecutive days. If contact was not possible after 3 attempts, the subject was excluded from the study. Interviewers did not inform the subject about the purpose of the study before filling out the questionnaire. Data from 1180 women were obtained. Randomly selected interviews (more than 10%) were checked by the principal investigators by phone calls.

Abbreviations used in this paper: BMI, body mass index; GERD, gastroesophageal reflux disease.

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We used a previously validated reflux questionnaire,[7,8] which was translated into Turkish and adapted to the local culture.[9] Details of the questionnaires and domains captured by the survey can be found elsewhere.[6,9] Each major symptom (heartburn, regurgitation, dysphagia, chest pain) was scored for frequency and severity. It was previously defined by Locke et al[7] that the group with frequent symptoms, defined as heartburn and/or regurgitation occurring at least once a week or common, was accepted as having GERD. The group with occasional symptoms was defined by us and others as that of an episode of one of the major symptoms less than once a week during the past year.[6,10] More questions were added related to the aim of the study such as the number of pregnancies, curettages, abortions, the date of the last delivery, number of all pregnancies and completed pregnancies (pregnancies ending with live or dead births), and the existence of heartburn or acid regurgitation for each pregnancy.

Statistical Analysis

Comparison of normally distributed numeric data between 2 groups was performed with Student *t* test for independent groups. When 3 groups were to be compared, one-way analysis of variance was used for global comparison, and then pairwise group comparisons were done with Tukey honestly significant difference tests. The association of independent variables, ie, number of pregnancies, presence of heartburn in pregnancies, body mass index (BMI), with GERD was studied for whole study group and also for four 10-year age strata, including 18–24, 25–34, 35–44, and 45–49 years of age. Also, logistic regression models with the presence of GERD as dependent variable were built. In these models, variables that were considered, a priori, to be related with the presence of GERD, and also age and BMI were entered as predictors. When the significance of the examined factor was found to be significant with the analysis of a model including age and BMI, then this factor was called a significant and age- and BMI-independent predictor for the probability of the presence of GERD. Statistical significance level was assigned to *P* values less than .05 except post hoc multiple pairwise comparisons. For these situations, Bonferroni modification for type I error level was performed. Statistical Package for Social Sciences (SPSS version 9.0; SPSS Inc, Chicago, IL) was used for data entry and statistical analysis.

Results

Demographics and Response Rate

The questionnaire was applied to 1180 women from October 2002–June 2004. Mean (± standard deviation) age was 35.4 ± 8.1 years. Age distribution and prevalence of GERD for each age group are shown in Table 1. The prevalence of GERD significantly increased with age. The majority of the population were housewives (75.8%); others were workers (10.9%), government employees (6.4%), self-employed (1.7%), and retired (5.1%). The number of completed pregnancies is shown in Table 2. About 40% of the population had more than 2 deliveries, and 11.8% had more than 5 and up to 10 deliveries. Median delivery was 2 ± 1.2 (range, 1–10).

Table 1. Age Distribution, Education Level, BMI, and Prevalence of GERD

			GERD		
		Total	n	%	*P* value
	Total	1180	87	7.4	
Age (*y*)	18–24	97	2	2.1	<.001
	25–34	468	21	4.5	
	35–44	405	38	9.4	
	45–49	208	26	12.5	
Education	University	63	2	3.2	<.001
	High school	252	8	3.2	
	Secondary school	290	17	5.9	
	Primary school	476	47	9.9	
	Literate	41	5	12.2	
	Illiterate	57	8	14.0	
BMI	Underweight, ≤18.5	27	1	3.7	<.001
	Normal, 8.6–24.9	547	28	5.1	
	Overweight, 25.0–29.9	428	32	7.5	
	Obese, 30.0–39.9	141	18	12.8	
	Morbidly obese, ≥40	14	3	21.4	

NOTE. *P* values denote the significance of the association between the presence of GERD and the variables in the table. The total number of subjects is slightly different than the sum of the subgroups because of the missing values (2 for age, 1 for education, and 23 for BMI).

Prevalence of Classic and Extraesophageal Symptoms

The prevalence of frequent and occasional GERD symptoms was 4.5% and 12.2%, respectively, for heartburn and 5.3% and 18.7%, respectively, for regurgitation within the last year (Figure 1). The prevalence of GERD (frequent heartburn or regurgitation at least weekly within last year) was 7.4%. Interestingly, the prevalence of GERD was inversely related with education. For example, only 3.2% of subjects graduated from university; however, 14% of illiterate subjects had GERD ($P <$ .001). Age and BMI were also significantly related with GERD in univariate analysis (Table 1). As it has been shown in our previous studies,[6] subjects with frequent GERD symptoms have more common additional symptoms such as noncardiac chest pain, dyspepsia, dysphagia, hiccups, nausea, vomiting, belching, cough, hoarseness (either frequent or occasional) compared with subjects without GERD in all parameters. All symptoms except vomiting were more common in subjects with frequent symptoms compared with occasional symptoms.

Deliveries and the Risk of Gastroesophageal Reflux Disease

The risk of GERD had been increased tremendously by the number of completed deliveries. Whereas women with a history of just one delivery had a very low chance of GERD (1.5%), more than 2 deliveries were accompanied with a very high chance of GERD (15.1%; $P <$ .001) (Table 2). In the group with no heartburn during pregnancy only 5.5% had GERD ($P <$ .001). If there was heartburn during any of the pregnancies; the prevalence of GERD was 17.7%. More than 2 pregnancies with a history of heartburn were accompanied by a 36.1% chance of having GERD. If we look at the data in another way, the prevalence of heartburn during pregnancy was 6.4% if there was

Table 2. Number of Completed Pregnancies, Presence of Heartburn and Regurgitation During the Pregnancy, and Prevalence of GERD

		Total (n = 1180)	GERD (n = 87)	%	*P* value
No. of completed pregnancies	1	390	6	1.5	<.001
	2	531	42	7.9	
	>2	259	39	15.1	
Occurrence of heartburn during pregnancy	No	999	55	5.5	<.001
	Yes	181	32	17.7	
No. of pregnancies with heartburn	1	78	5	6.4	<.001
	2	67	14	20.9	
	≥3	36	13	36.1	
Occurrence of regurgitation during pregnancy	No	775	38	4.9	<.001
	Yes	405	49	12.1	
No. of pregnancies with regurgitation	1	189	10	5.3	<.001
	2	158	22	13.9	
	≥3	58	17	29.3	

NOTE. *P* values denote the significance of the association between the presence of GERD and the variables in the table.

no GERD and 36.8% if GERD currently existed ($P < .0001$). Subjects were also evaluated for the presence or absence of heartburn during pregnancy and the existence of GERD. We also checked the risk of GERD in high multiparous women (>4) compared with women with less than 5 pregnancies. In a total of 113 women identified with more than 4 deliveries, the prevalence of GERD was 26.5%. The prevalence of GERD in the group of women with less than 5 deliveries was 7.0% (odds ratio, 1.27; $P = .000000001$).

An important point was related to whether the relationship between heartburn during pregnancy and the increasing risk of having GERD are related to aging, increase in BMI, or prepregnancy heartburn (carrying their GERD to their second, third, etc pregnancies until the present).[11] We performed logistic regression analysis to control for the effects of different confounding factors. It was clear that educational status, age, and BMI lost their significant effect in this multivariate analysis. Only the number of pregnancies and the number of episodes of heartburn/regurgitation during pregnancy kept their significance (Table 3). The effects of BMI and age are shown according to age stratification in Table 4. Nearly all groups showed that the risk increased at least 3 times compared with the subjects without heartburn during pregnancy.

In this retrospective study it is possible that subjects currently having GERD were more likely to recall their heartburn during pregnancy, demonstrating recall bias. In this case if the time after the last pregnancy was very long, the risk of recall bias would be higher. To understand the effect of possible recall bias, we classified subjects into 3 groups according to the date of last completed pregnancy. Prevalences of GERD in subjects who experienced their last pregnancy within 2 previous years (who are probably the subjects with minimal recall bias, if any) were 13.8% and 2.5% for subjects with and without heartburn during pregnancies, respectively. This association between heartburn during pregnancies and current GERD was consistent among all subgroups defined by the time after the last completed pregnancy; GERD risks were 3.5% vs 13.3% for 3–10 years and 8.9% vs 30.4% for longer than 10 years.

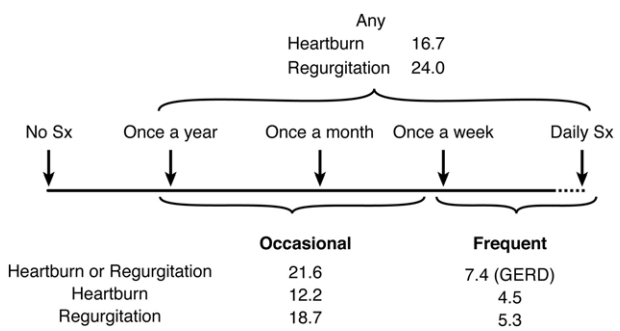

Figure 1. Prevalence of GERD symptoms (%).

Medications, Smoking, Alcohol Consumption

Subjects with GERD were taking antacids, H_2 receptor antagonists, or proton pump inhibitors (43.7%) at a higher rate than subjects without symptoms (16.2%, $P = .001$). Subjects with occasional symptoms were consuming these medications as commonly as subjects with frequent symptoms (39.6%). Antacids were taken by subjects with both occasional (29.0%) and frequent (18.4%) symptoms significantly more frequently than

Table 3. Logistic Regression Analysis for the Prediction of GERD

Variable	*P* value	Odds ratio (95% confidence interval)
No. of completed pregnancies	.05	
No. of pregnancies = 1 vs 2	.02	3.04 (1.19–7.72)
No. of pregnancies = 1 vs >2	.025	3.39 (1.16–9.86)
No. of pregnancies with heartburn	.0002	1.54 (1.23–1.94)
No. of pregnancies with regurgitation	.002	1.35 (1.11–1.64)
Educational status	.51	NA
Age	.17	1.03 (0.99–1.06)
BMI	.27	1.03 (0.98–1.09)

NOTE. The dependent variable is the presence of GERD. The categorical predictors are number of completed pregnancies and education status. Other predictors are in numeric scale. All predictors were entered into the model all together. Because educational status is a categorical variable, an overall odds ratio was not calculated.

Table 4. Prevalence of GERD in Subgroups Defined by the Presence of Heartburn During Pregnancy, Age, and BMI

Age (*y*)	BMI	Heartburn during pregnancy: Absent	Heartburn during pregnancy: Present	Odds ratio (95% confidence interval)	*P* value
25–34	<25	2.8	8.9	3.34 (0.94–11.94)	.07
	≥25	3.0	12.5	4.68 (1.10–19.84)	.045
35–44	<25	2.9	33.3	16.75 (3.52–79.61)	.001
	≥25	8.5	27.3	4.06 (1.77–9.30)	.001
45–49	<25	11.5	33.3[a]	3.86 (0.31–48.24)	.34
	≥25	8.8	31.3	4.71 (1.38–16.04)	.02

[a]Number of subjects = 3. Number of subjects in all other groups was from 15–247.

by subjects without symptoms (9.5%) ($P < .05$). Frequent symptoms occurred in 7.6% of nonsmokers compared with 7.0% in smokers ($P > .05$), and similar results were found with alcohol consumption (7.2% vs 13.5%; $P > .05$). Only 37 subjects were drinking alcoholic beverages, and all were drinking these less than 3 times per week.

Discussion

In the present study we aimed to evaluate the predisposing effect of heartburn during pregnancy on postpregnancy GERD which is a relatively underestimated issue. Our results showed that the prevalence of GERD was lower (7.4%) in this study than the prevalence of GERD in Turkey (22.7%) (Bor et al, unpublished data) and in the area of Bornova, Izmir (20%).[6] However, the comparison with the age stratification for women revealed different results than our previous study. The prevalence increased by age 2–5 times according to the age in the present study. Because the major difference comparing the same age groups between these 2 studies was excluding the nulliparous women in the current study; even in a younger population the prevalence of GERD was higher. The relationship between the number of deliveries and the prevalence of GERD was obvious. GERD prevalence was 1.5% with 1 delivery, and an impressive, cumulative increase was observed with more than 4 deliveries (22.2%). A similar relationship was observed with the number of pregnancies with heartburn and the prevalence of postpartum GERD. The prevalence of GERD increased from 6.4% to 36.1% with increasing number of completed pregnancies with heartburn and from 5.3% to 29.3% with regurgitation. This effect cannot be explained by aging or obesity because our logistic regression analysis showed that the effect was not related with aging, BMI, and educational status. Factors related with the risk of GERD were number of completed pregnancies and number of heartburn/regurgitation during pregnancies.

Generally the number of studies is very low and inadequate with reference to heartburn/GERD and pregnancy. It has long being known that the prevalence of heartburn increases during pregnancy; however, it has also been accepted as an innocent condition. Irrespective of the severity, all of the symptoms immediately disappeared with labor, and the majority of patients did not exhibit erosive esophagitis. Extraesophageal manifestations of GERD are believed to be lower than expected; however, no data have been published addressing the frequency of symptoms other than heartburn during pregnancy.[5] Marrero et al[11] showed that the prevalence and severity of heartburn also steadily increased during pregnancy; 22% complained of heartburn during the first, 39% during the second, and 72% during the third trimester ($P < .001$). The risk of heartburn increased with gestational age, prepregnancy heartburn, parity, and inversely with maternal age. BMI before pregnancy, weight gain during pregnancy, or race was not predictive of heartburn frequency or severity.[11] Bainbridge et al[2] indicated that symptoms were increased in multiparous women compared with primiparous women such as in the present study, and whenever heartburn was present during the first pregnancy, it was likely to recur during subsequent pregnancies.

Pathogenetic factors such as increased hormones and their effects on lower esophageal sphincter and increased intra-abdominal pressure have been studied. The majority of the studies in pregnant women were performed by measuring lower esophageal pressure. Some studies have shown a significant drop,[12,13] whereas others have not.[14,15] Studies have shown the amplitude of esophageal peristaltic changes in pregnancy; however, either the number of patients was too small, or the quality of studies was low. Al Amri[16] evaluated 24-hour intraesophageal pH monitoring in 8 symptomatic women during and after pregnancy. Results showed that lower esophageal sphincter pressure was significantly lower during late pregnancy and returned to normal at postpartum. In addition, there were more reflux in upright posture and more frequent acid reflux during late pregnancy compared with postpartum. However, the percentage below pH <4 was not significantly reduced, and actual figures were 6.4 ± 5.4 (range, 0.4–15.8) during pregnancy to 5.1 ± 6.5 (range, 0.5–19.8) at about 10 weeks after delivery. This result implies that after the pregnancy there was still pathologic reflux in this group of women.[16]

We conclude that the risk of GERD increased by having heartburn during pregnancy. It is hard to speculate about the possible mechanisms of this effect. One possibility might be the long contact time of the esophagus with the gastric contents during the period of pregnancy or consecutive pregnancies. This might predispose or sensitize the tissue to having the disease in the future. Studies by Arkar et al[17] have suggested that esophageal sensitization can occur with prior acid exposure. They showed that acid infusion into the distal esophagus reduces pain threshold in both the exposed and the nonacid exposed esophagus, suggesting that hyperexcitability within the central visceral pain pathway (central sensitization) might contribute to the development of the hypersensitivity. Another possibility is the mechanical effects of distention of the abdominal cavity at the pregnancy, which might have an effect on the integrity of the antireflux barrier, and this might specifically disrupt the hiatus.

The major limitation of our present study is the retrospective design. It might be difficult to recall the symptoms present at the pregnancy, especially for the consecutive pregnancies. However, we observed that generally women did not have great difficulties in remembering the symptoms during pregnancy possibly for 2 reasons; pregnancy is an important, remembered period in their life, and they would tolerate all these severe symptoms without taking powerful medications. With the heartburn and/or regurgitation predisposition for having GERD; one might design a cohort study evaluating women

before pregnancy and following them for many years after the birth of their children.

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