In vitro fertilization-induced pregnancies predispose to gastroesophageal reflux disease

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Abstract

Background: Women conceiving following in vitro fertilization (IVF) likely have a variety of risk factors that predispose them to gastroesophageal reflux disease (GERD) in the future.

Objective: We aimed to investigate whether pregnancy through IVF may predispose to subsequent GERD compared with pregnancies without IVF. We also evaluate whether twin IVF pregnancies lead to additional risk for having GERD compared with singleton IVF pregnancies.

Methods: A validated reflux questionnaire was administered to 156 women with singleton ($n=102$) or twin ($n=54$) IVF birth (IVF group) and 111 women with a naturally conceived singleton birth (control group). All women included in the study were primiparas who had given birth at least 1 year prior to data collection. The diagnosis of GERD was based on the occurrence of typical symptoms (heartburn, regurgitation, or both) at least once a week.

Results: The prevalence of GERD was 13.5% and 4.5% in IVF and control groups ($p=0.015$); in the IVF group, this was slightly higher, but not statistically significant, in women with twin compared with singleton pregnancies (14.8% vs. 12.7%, $p=0.749$). Logistic regression analysis showed that IVF was strongly associated with subsequent GERD (OR, 3.30; 95% CI 1.20–9.04; $p=0.02$).

Conclusion: The risk of developing GERD at least 1 year after delivery increased following IVF. Long-term follow-up studies are required to determine whether therapy during pregnancy can prevent this risk.

Keywords

Gastroesophageal reflux disease, heartburn, regurgitation, in vitro fertilization, pregnancy

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Introduction

Gastroesophageal reflux disease (GERD), commonly experienced as heartburn, regurgitation, or both, frequently occurs during pregnancy; prevalence estimations, commonly based on questionnaires, show a wide range of 25–80%,^{1,2} with a mean of 50% in general. Few longitudinal studies have addressed the nature and prevalence of GERD symptoms during pregnancy, with variable results; regarding the frequency of GERD symptoms during pregnancy, one study showed a similar incidence,³ and others indicated an increase⁴ or decrease.⁵ Risk factors for pregnancy-related GERD include gestational age, heartburn before pregnancy, and multiparity.^{3,6} Cumulative weight gain during pregnancy is a risk factor in the third trimester;³ increased maternal age apparently has a protective effect.⁶

The etiology of GERD during pregnancy is most likely decreased lower esophageal sphincter (LES) pressure caused by increased progesterone levels during pregnancy.⁷ Although basal LES pressure may not

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change during the first trimester, it gradually decreases to 33–50% during advanced pregnancy, reaching a nadir at 36 gestational weeks.^{8,9} Although a controversial issue, increased abdominal pressure due to an enlarging gravid uterus may play a role.¹⁰

Because complications caused by reflux during pregnancy rarely occur, and heartburn disappears almost completely after delivery, gestational GERD symptoms are considered temporary. Atypical extraesophageal manifestations of GERD and complications of mucosal damage such as esophagitis, stricture, and Barrett's esophagus are rare during pregnancy.¹⁰ However, we have shown that reflux symptoms during pregnancy predispose to subsequent GERD.¹¹ Further, the risk steadily increases with the number of pregnancies in women with heartburn (5.5% in those without heartburn, 17.7% in those with GERD symptoms during any pregnancy, and 36.1% in those with GERD symptoms during more than two pregnancies).¹¹ Moreover, pregnancy has been found to be a risk factor for GERD 1 year postpartum.³

Women conceiving following in vitro fertilization (IVF) likely have risk factors such as stress, medications (aspirin, progesterone, and estrogen), immobilization, and weight gain during pregnancy that might predispose them to subsequent development of GERD at least 1 year after delivery. To investigate this, we conducted a retrospective study among a cohort of women who gave birth once (singleton or twin) with IVF at least 1 year prior to data collection (IVF group). Study participants completed validated questionnaires that asked about symptoms of GERD during the previous year and during and before their pregnancy. We compared them with an age-matched control group with a naturally conceived singleton birth (without IVF) that was derived from our previous study.¹¹ We also investigated whether women with twin IVF pregnancies may have an additional risk of having GERD compared with those with singleton IVF pregnancies, mainly due to a notable increase in intra-abdominal pressure and volume during their pregnancy.

Patients and methods

Study population

Subjects were recruited from a cohort of 1303 who conceived following IVF at two referral hospitals with IVF programs in Izmir, Turkey (Ege University Family Planning and Infertility Research and Treatment Center, and Irenbe IVF Center). The prevalence of GERD in this region is similar (20%) to that in other developed countries.¹² We included women who conceived following IVF, gave birth once (singleton or twin

birth) more than 1 year earlier, and resided in Izmir with a confirmed address. We excluded women if they delivered more than once, died, moved from Izmir before the interview, were pregnant, had psychiatric diseases, refused to complete the survey, or gave an incorrect address or name.

Data collection

The study was conducted through face-to-face interview by two experienced interviewers^{11,12} who made three attempts to contact potential participants. All subjects in the study were informed verbally, and their permission was obtained to complete questionnaires. Subjects were not informed of the study's purpose before filling in the questionnaire. At least 10% of randomly selected interviews were reviewed by the principal investigators, who contacted subjects by phone.

Questionnaire, definitions, and variables

We used a validated reflux questionnaire adapted from Locke et al.¹³ that was translated into Turkish, linguistically validated, and adapted to the local culture.¹⁴ Details of the questionnaire have been published.^{12,14} Major symptoms (heartburn and regurgitation) were scored for frequency and severity. The questionnaire also included questions regarding whether these symptoms were experienced during and before their pregnancy. It was previously defined by Locke et al.¹³ that the group with frequent symptoms, defined as heartburn and/or regurgitation occurring at least once a week or common during the past year, was accepted as having GERD. More questions were added related to the aim of the study, such as the number of fetuses (single or twin), weight gain during pregnancy, delivery type, newborn weight, delivery date, use of antacids and other medications during pregnancy, preterm birth, vaginal bleeding during pregnancy, and nausea/vomiting during pregnancy.

Control group

We have previously studied whether the presence of GERD symptoms during pregnancy predisposes women to GERD in the future.¹¹ In that study, same reflux questionnaire was applied to 1180 randomly selected women aged 18–49 years who had given birth (without IVF) at least 1 year prior to data collection and that study was performed in the same city. The data of age-matched control group among 390 women with one completed pregnancy were derived, serving a control group, from that study. Because the number of pregnancies confers an

increased risk of GERD,¹¹ only women with one completed pregnancy were included.

Statistical analysis

Descriptive statistics are presented as mean and standard deviation (SD) for numerical variables and as frequencies and percentages for categorical variables. Pearson χ^2 or Fisher's exact tests were used to compare categorical variables. For continuous variables, differences between groups were evaluated using the Student *t*-test for normally distributed data or the Mann-Whitney test for data not normally distributed. Univariate logistic regression analysis was performed to calculate the odds ratio (OR) and 95% confidence interval (CI) for having subsequent GERD in the setting of IVF. In determining the risk factors for GERD, age, delivery type, newborn weight, regurgitation before pregnancy, regurgitation during pregnancy,

heartburn before pregnancy, heartburn during pregnancy, and use of non-steroidal anti-inflammatory drugs were the significant variables to be included in the model. However, age, delivery type, and newborn weight variables were excluded from the model as they were confounding variables of IVF. Accordingly, a model including the pregnancy type variable was developed using univariate regression analysis. Statistical significance level was defined as $p < 0.05$. The Statistical Package for Social Sciences (SPSS version 15.0; SPSS Inc, Chicago, IL) was used for data entry and analysis.

Results

Among 1303 women who conceived following IVF, 377 met the inclusion criteria on first screening of hospital records. After a telephone survey, we excluded 221 (Figure 1). The questionnaire was administered to

Figure 1. Flow diagram of enrollment of study subjects.

*Control group included women with a naturally conceived singleton birth. A group of women who conceived naturally and gave twin birth was not included, because it was very difficult to find such a group.

156 women who conceived following IVF with one birth (IVF group); of these, 102 and 54 gave singleton birth and twin birth, respectively; 111 subjects with a naturally conceived singleton birth were selected from our previous study¹¹ as the control group (Figure 1). A group of women who conceived naturally and gave birth to twins was not included, because it was very difficult to find such a group.

The mean $\pm$ SD age of the study population was 32.9 ± 7.1 years; 43% were aged between 25 and 34 years of age. The majority were housewives (58.3%). The median time since delivery was 4 years (range, 1–33 years). Demographic data are shown in Table 1. Age, body mass index, work status, and smoking rates were not significantly different between groups. Educational status was higher in the IVF group.

IVF and risk of GERD

The prevalence of GERD was 9.7% in the study population and 13.5% and 4.5% in IVF and control groups, respectively ($p=0.015$). Table 2 shows the GERD prevalence in subgroups. Frequent heartburn and regurgitation were significantly more common in the IVF group compared with the control group (IVF group: 10.3% and 8.3%, control group: 1.8% and 3.6%, respectively). In the IVF group, the prevalence of GERD was slightly higher, but not statistically

significant, in women with twin birth compared with those with singleton birth (14.8% vs. 12.7%, $p=0.749$).

There was no statistically difference between women with or without GERD as a function of delivery type, newborn weight, and weight gain during pregnancy. The rate of vaginal delivery was 19.2% in women with GERD compared with 41.4% for those without GERD ($p=0.087$). Mean weight of newborn was 2816.2 ± 673.0 g vs. 3007.2 ± 637.9 g ($p=0.156$) in women with or without GERD, respectively. Weight gain during pregnancy was 11.5 ± 8.4 kg vs. 15.1 ± 6.3 kg ($p=0.253$) in GERD versus non-GERD women. Subjects with GERD took acid suppressive therapies at a higher rate compared with subjects without GERD symptoms (65.4% vs. 28.4%, $p<0.001$).

Univariate logistic regression analysis showed that IVF was strongly associated with subsequent GERD (OR, 3.30; 95% CI 1.20–9.04; $p=0.02$).

Analysis of factors possibly contributing to predisposing individuals to GERD in the IVF group

Since we found a higher rate of GERD in women who conceived following IVF, a univariate analysis was performed in the IVF group to identify potential risk factors that predispose these women to subsequent GERD. Vaginal bleeding during pregnancy, preterm delivery risk or preterm birth, nausea/vomiting, and weight loss due to nausea/vomiting were assessed. Nearly half of mothers who conceived following IVF experienced these events during their pregnancies. However, only increased weight loss due to nausea/vomiting significantly increased in subjects with GERD (Table 3).

The GERD rates during and before pregnancy

The prevalence of GERD before pregnancy in the IVF group was higher compared with the control group (7.1% vs. 3.6%, $p=0.523$), but the difference was not significant. The prevalence of GERD during pregnancy in the IVF group was greater by a factor of approximately 2 compared with that in the control group (42.9% vs. 22.5%, $p=0.008$) (Figure 2).

Table 1. Demographic data of subjects

	IVF group (n = 156)	Control group (n = 111)	p-value
Age, years (%)			
Age groups			
18–24	0.6	2.3	0.11
25–34	34.4	32.2	
35–44	61.0	55.6	
45–54	3.9	9.9	
Education (%)			
University	41.0	20.7	<0.001
High school	24.4	30.6	
Secondary school	4.5	19.8	
Primary school	28.2	23.4	
Literate	0.6	3.6	0.58
Illiterate	1.3	1.8	
Body mass index, mean $\pm$ SD	25.6 ± 4.8	26.4 ± 4.9	
Work status (%)			
Housewife	57.1	52.6	0.71
Worker	41	47.4	
Smoking (%)	41.7	41.3	0.96

Table 2. Prevalence of GERD in the study population

Groups	Total (n = 267)	GERD (n = 26)	%	p-value
Singleton IVF birth	102	13	12.7	0.048
Twin IVF birth	54	8	14.8	
Singleton natural birth (control)	111	5	4.5	

Discussion

Heartburn during pregnancy predisposes women to subsequent GERD, indicating that pregnancy-related GERD is not a transient and inconsequential condition.¹¹ Here, we hypothesize that women who

conceived following IVF may have an additional risk of subsequent GERD. Therefore, we compared women who conceived following IVF with those with a naturally conceived singleton birth. The prevalence of GERD symptoms was significantly higher in women with singleton or twin IVF birth compared with those with a naturally conceived singleton birth. No significant difference was found in the IVF group between women who gave singleton birth or twin birth.

The estimated prevalence of GERD in IVF and control groups is lower than the prevalence in Turkey (22.8%)¹⁵ and Izmir (20%);¹² this may be explained by the relatively younger age (mean approximately 33 years) of our subjects. Another possibility is the lower number of pregnancies in our study population, because an increasing number of pregnancies is a confirmed risk of GERD.¹¹

The present findings suggest that conceiving following IVF is associated with an increased risk of GERD for at least 1 year after delivery. Women undergoing IVF likely have a number of potential risk factors that predispose to GERD. First, medications used in IVF may contribute to predispose individuals to GERD. For example, progesterone during the first 6–8 gestational weeks and aspirin are almost universally administered for IVF; estrogen supplementation is

Table 3. Univariate analysis of possible risk factors for GERD in the IVF group

	GERD (n = 21)	Non-GERD (n = 135)	p-value
Preterm birth (%)	38.1	45.9	0.502
Vaginal bleeding during pregnancy (%)	42.9	50.4	0.522
Preterm birth risk during pregnancy (%)	57.1	37.0	0.080
Nausea/emesis during pregnancy (%)	57.1	45.2	0.307
Beginning month of nausea/vomiting (mean $\pm$ SD)	1.9 $\pm$ 1.2	1.9 $\pm$ 0.9	0.798
Weight loss due to nausea/vomiting (%)	23.8	8.3	0.047

Figure 2. The prevalence of GERD before, during and after pregnancy in subjects with or without IVF.

also used. Studies in humans and animals show that increased circulating levels of progesterone, either alone or in combination with estrogen during pregnancy, mediate LES relaxation, which is regarded as the most important mechanism in the pathophysiology of GERD during pregnancy.¹⁶ Moreover, in non-pregnant women, resting LES pressure decreases significantly following sequential treatment with an oral contraceptive; in pregnant women, resting LES pressure decreases progressively during pregnancy, reaching a nadir at 36 gestational weeks and returning to normal postpartum.^{9,17} However, physiological concentrations of progesterone do not affect LES pressure and 24-h ambulatory esophageal pH levels (pH <4) during the normal menstrual cycle.¹⁸ The effects of progesterone and estrogen during pregnancy on LES relaxation may be further enhanced by high doses of progesterone and estrogen during IVF cycles. This clearly requires further research. Notwithstanding the unclear role of aspirin in the symptomatology of GERD, aspirin use is associated with GERD symptoms in some population-based studies.^{19,20}

Second, women undergoing IVF may spend considerable time in a supine or dorsal recumbent position due to fear of miscarriage. Thus, recumbent reflux may contribute to predisposition to GERD. The supine position likely contributes to impaired esophageal acid clearance;²¹ however, no relevant controlled studies are available. Finally, stress may contribute to GERD symptoms in women with IVF pregnancies experiencing stress related to fertility and who suffer from increased levels of depression and anxiety.²² Indeed, major life stressors predict symptom exacerbation in patients with heartburn.²³

Increased intra-abdominal pressure caused by an enlarging gravid uterus may contribute to the increased incidence of GERD during pregnancy,²⁴ but this is not supported by other studies.^{25,26} We expect that women with twin birth may have an additional risk of subsequent GERD, mainly due to a notable increase in intra-abdominal pressure during their pregnancy. However, although there was an increase, we did not detect a significant difference between women with singleton birth and those with twin birth in current GERD prevalence. This finding might support the conclusion that a compensatory increase in LES pressure occurs with increased intra-abdominal pressure.^{25,26}

We noticed that weight gain during pregnancy was slightly lower, but not statistically significant, in women with GERD compared with those without. This may be explained by weight loss during the first trimester due to nausea/vomiting in women with GERD who underwent IVF. In fact, weight loss due to nausea/vomiting was found only risk factor for GERD in IVF group in univariate analysis (Table 3).

The prevalence of GERD during pregnancy in the IVF group was greater by a factor of approximately 2 compared with that in the control group (42.9% vs. 22.5%). Univariate logistic regression analysis showed that pregnancy with IVF increased the risk of having subsequent GERD 3.3 times (95% CI 1.20–9.04). This may be explained by prolonged contact of the esophagus with gastric contents due to decreased LES pressure or a diminished LES response during IVF pregnancy, and may predispose or sensitize tissue to future disease. More remote episodes of reflux may confer increased sensitivity on esophageal nociceptors to subsequent acid exposure.^{27,28} Acid-induced esophageal sensitization (chemosensitivity) can persist despite prolonged acid suppression and resolution of macroscopic inflammation.²⁹

The present study has several limitations: (1) the study design was retrospective; (2) sample size was small; and (3) a validated symptom-based questionnaire was used for diagnosing of GERD. According to the Montreal definition of GERD, the disease may be diagnosed based on typical symptoms alone or on the basis of investigations (e.g. pH testing, impedance monitoring, endoscopy, histology, or electron microscopy).³⁰ The symptom-based questionnaires have been used in many epidemiological studies (including our studies in Turkey)¹² that assessed the prevalence of GERD.³¹ In the current study, since we also asked about GERD symptoms during and before pregnancy, questionnaire-based assessment of GERD was the only possible diagnostic methodology. (4) There may be a recall bias for GERD symptoms. It might be difficult to recall the symptoms at the time of the completion of the questionnaire for pregnancy and pre-pregnancy periods. However, we observed that generally women did not have great difficulties in remembering the symptoms during pregnancy, possibly due to two reasons: pregnancy is an important, remembered period in their life, and they would tolerate all these severe symptoms without taking powerful medications. We showed that recall bias was not an important factor in our previous study.¹¹ Those findings implicate that potential effect of recall bias on the results of current study is minimal. (5) A group of women who conceived naturally and gave birth to twins was not included, because it was very difficult to find such a group.

In conclusion, the risk of developing GERD at least 1 year after delivery increased following IVF. There was no difference between women with singleton birth and those with twin birth in terms of developing subsequent reflux symptoms. Further long-term follow-up studies are required to determine whether therapy during pregnancy can prevent this risk.

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Conflict of interest

None declared.

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