Reproductive Medicine; *Endocrinology and Infertility*

Evaluation of Nausea and Vomiting Severity in Pregnancies Conceived Through Assisted Reproduction

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ABSTRACT

OBJECTIVE: This study aimed to evaluate the severity of nausea vomiting of pregnancy in assisted reproductive technologies pregnancies using the Pregnancy-Unique Quantification of Emesis scoring system which is a validated, clinically relevant method to assess nausea vomiting of pregnancy severity.

STUDY DESİGN: A total of 101 pregnant women between 8+0-14+6 weeks of gestation were enrolled in this case-control study. Of these women, 53 had pregnancies conceived via assisted reproductive technologies (study group) and 48 had pregnancies conceived naturally (control group). The Pregnancy-Unique Quantification of Emesis-24 scale was utilized to evaluate nausea vomiting of pregnancy severity in both groups. Weight change during pregnancy and hospital admission due to nausea vomiting of pregnancy were also compared to assess severe nausea vomiting of pregnancy.

RESULTS: According to the Pregnancy-Unique Quantification of Emesis scale, 67.9% of patients with assisted reproductive technologies pregnancies experienced mild nausea vomiting of pregnancy while 24.5% had moderate and 7.5% had severe nausea vomiting of pregnancy. In the spontaneous pregnancies group, 60.4% experienced mild nausea vomiting of pregnancy, 33.3% had moderate nausea vomiting of pregnancy and only 6.3% had severe nausea vomiting of pregnancy. The overall Pregnancy-Unique Quantification of Emesis score was 5 (3-8.5) in assisted reproductive technologies pregnancies and 5 (3-10) in spontaneous pregnancies (p=0.650). There was no statistically significant difference regarding hospitalization history due to nausea vomiting of pregnancy between assisted reproductive technologies and naturally-conceived pregnancies (p=0.619).

CONCLUSION: Conception using assisted reproductive technologies does not increase nausea vomiting of pregnancy severity. Furthermore, weight change during pregnancy and hospitalization rates due to nausea vomiting of pregnancy were comparable between women conceived with assisted reproductive technologies and women with natural conception.

Keywords: Assisted reproductive techniques, Hyperemesis gravidarum, Nausea, Pregnancy, Pregnancy-unique quantification of emesis, Vomiting

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Introduction

Nausea and vomiting of pregnancy (NVP) is a common medical problem affecting up to 80% of all pregnant women. The severity of NVP can vary widely from mild form seen in most pregnancies to a severe condition with intractable vomiting, dehydration, and electrolyte imbalance called hyperemesis gravidarum (HG) (1). The Pregnancy-Unique Quantification of Emesis (PUQE) scoring system is a validated, clinically relevant method to assess the severity of NVP (2,3). The PUQE scale shows a strong correlation with rates of hospitalization for NVP, ability to take multivitamins, women's self scores of wellbeing, and health cost of NVP (3). The original PUQE measures the symptom severity over the previous 12 hours. Several researchers modified the original version to assess the symptoms over a wider period of pregnancy (4,5).

The etiology of NVP remains unknown. However, much research has focused on endocrine factors in the pathogenesis of NVP. The levels of reproductive hormones change dramatically during pregnancy (6). Changes in the concentrations of human chorionic gonadotropin (hCG), estradiol, and progesterone have been suggested to play a role in the pathogenesis of NVP.

The number of pregnancies achieved through assisted reproductive technologies (ART) has increased significantly over the last decades (7). Despite this increase, few studies questioned the severity of NVP in ART pregnancies compared with spontaneous pregnancies. Hormone treatment and the presence of multiple corpora lutea during the first trimester are the major differences between ART pregnancies and spontaneous pregnancies (8). Thus, it is plausible that pregnancies conceived through ART have an altered hormonal milieu. Many studies reported higher hCG levels in ART pregnancies (9-11).

We hypothesized that altered hormonal milieu and other factors as a result of ART procedures may influence the severity of nausea and vomiting in ART pregnancies and consequently, these women may require additional medical support. This study aimed to evaluate the severity of NVP in ART pregnancies using the PUQE scale and compare it with spontaneous pregnancies.

Material and Method

This case-control study has been approved by the Institutional Review Board of Kocaeli University, Kocaeli, Turkey (approval number: GOKAEK-2020/1.31 2020/24, approval date: 21.01.2020). All patients gave informed consent to participate in the study. This research was conducted in accordance with the ethical standards of the Helsinki Declaration and its later amendments.

This was an observational study conducted at Kocaeli University Department of Obstetrics and Gynecology from February to May 2020. The study group comprised pregnant women between 8+0-14+6 weeks' gestation who conceived through ART at Kocaeli University ART Clinic. The control group included women who conceived naturally, attending our outpatient clinic for routine antenatal care. The eligibility criteria for the study group were achieving pregnancy in a fresh cycle and a gestational age between 8+0-14+6 weeks. The eligibility criteria for the control group consisted of healthy pregnancies with gestational age between 8+0-14+6 weeks. Women with an acute infection such as gastroenteritis or urinary tract infection and any gastrointestinal, endocrine, or metabolic condition which may cause nausea and vomiting were excluded from the study. In the study group, patients less than 12 weeks gestation were using vaginal progesterone gel (Crinone 8%, Serono, United Kingdom) twice daily.

The 24-hour PUQE (PUQE-24) is a validated extension of the original PUQE questionnaire which assesses the severity of NVP over 24 hours (5). We used the PUQE-24 scale to evaluate nausea and vomiting severity in ART pregnancies. The PUQE-24 scale consists of three questions evaluating the duration of nausea and the number of episodes of vomiting and retching in a day. Every question has answers divided into 5 categories and scored from 1 to 5 depending on the severity of the symptom. Therefore, the total score ranges from 3 (no symptoms) to 15 (maximal symptoms). NVP is categorized as mild if the total score is less than 7, moderate if the total score is between 7 and 12, and severe if the total score is more than 12. Patients were asked to complete the PUQE-24 questionnaire and the PUQE-scores were compared between spontaneous and ART pregnancies.

Interviews were conducted in-person in the control group and either in-person or via phone calls in the study group. Patient characteristics including age, height, current weight, weight change during pregnancy, gravidity, parity, educational status, presence of any acute or chronic medical condition, and history of hospitalization due to NVP were also collected from the patients during the interviews.

Power analysis was conducted based on a study with a mean PUQE-score of 11 ± 3 in the group with HG and 9 ± 2.2 in the control group (3) and it was determined that 38 patients in each group would be required to detect a significant difference between groups with 90% power at a level of $\alpha=0.05$.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp, Armonk, NY, USA). Kolmogorov-Smirnov test was used to determine whether the variables follow the normal distribution. Continuous variables with normal distribution were expressed as mean±standart deviation (SD) while the continuous variables without normal distribution were expressed as median (25^{th}-75^{th} percentile). Categorical variables were expressed as numbers (percentage). Depending on the distribution of variables, either the Mann-Whitney U test or Student's t-test was performed to compare continuous variables. Chi-square analyses were used for the comparison of categorical variables. Variables with a statistically significant difference in univariate analysis were included in multinomial logistic regression analyses to determine the factors affecting the outcome variable. A p-value <0.05 was regarded as statistically significant.

Results

A total of 101 pregnant women between 8+0-14+6 weeks of gestation were enrolled in the study. Of these women, 53 had pregnancies conceived via ART and constituted the study group and 48 had pregnancies conceived naturally and made up the control group (Figure 1). The comparison of baseline characteristics of these women is shown in table I. There was no statistically significant difference between groups regard-

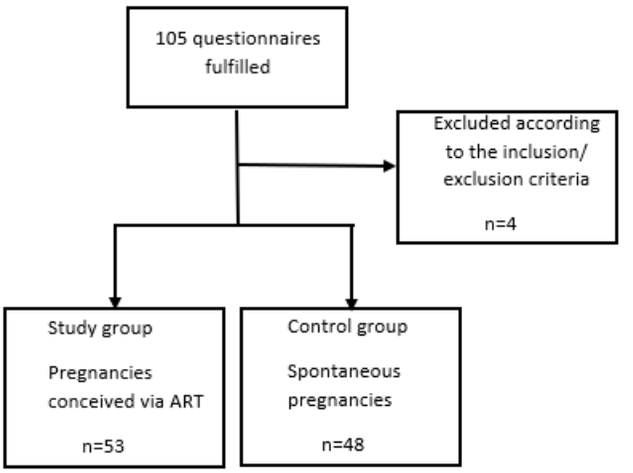

Figure 1: *The flowchart of the study*

ing age, body mass index (BMI), gestational week, and educational status. Women in the control group had significantly higher gravidity and parity compared to the study group ($p<0.001$ and $p<0.001$, respectively). The number of twin gestations was significantly higher in the study group than in the control group (30.2% vs. 4.2% respectively, $p=0.002$). In terms of a chronic medical condition, four patients in the study group had hypothyroidism. They were all receiving levothyroxine therapy and in euthyroid condition. The control group included one patient with mild asthma and one patient with hepatitis B carrier state.

Table II shows the comparison of PUQE scores among groups. The median score for the first question which evaluates the duration of nausea was 1 (1-3) in the ART pregnancies group and 2 (1-3.75) in the control group. There was no

Table I: *Baseline characteristics of the patients*

Characteristics	ART pregnancies (n=53)	Spontaneous pregnancies (n=48)	*p*
Age (y)	31.3± 4.9	29.5± 5.6	0.089[a]
Gravidity	1 (1-1)	2 (1-3)	**< 0.001[b]**
Parity	0 (0-0)	1 (0-2)	**< 0.001[b]**
Abortus	0 (0-0)	0 (0-1)	0.343[b]
BMI (kg/m2)	26.8± 5.6	25.8± 4.0	0.349[a]
Gestational week	12 (9-14)	10 (9-13)	0.088[b]
Type of pregnancy			
Singleton	37 (69.8%)	46 (95.8%)	**0.002[c]**
Twin	16 (30.2%)	2 (4.2%)	
Education			
Primary school	8 (15.1%)	10 (20.8%)	
Secondary school	7 (13.2%)	14 (29.2%)	0.066[c]
High school	27 (50.9%)	13 (27.1%)	
University	11 (20.8%)	11 (22.9%)	

Data are presented as mean±standard deviation, median (25th-75th percentile), or n (%), ART; Assisted reproductive technologies, BMI; Body mass index, [a]:Student's t-test, [b]: Mann-Whitney U test, [c]: Pearson chi-square test

Table II: *Evaluation of N/V according to the PUQE questionnaire*

Characteristics	ART pregnancies (n=53)	Spontaneous pregnancies (n=48)	*P*
PUQE Question1 (Duration of nausea)	1 (1-3)	2 (1-3.75)	0.397[a]
PUQE Question2 (Number of vomiting)	1 (1-2)	1 (1-2.75)	0.838[a]
PUQE Question3 (Number of retching)	2 (1-3)	2 (1-3)	0.204[a]
PUQE Score	5 (3-8.5)	5 (3-10)	0.438[a]
PUQE Score Severity			
Mild N/V (score <7)	36 (67.9%)	29 (60.4%)	
Moderate N/V (score 7-12)	13 (24.5%)	16 (33.3%)	0.650[b]
Severe N/V (score 13-15)	4 (7.5%)	3 (6.3%)	
Weight change during pregnancy (kg)	2 (0- 3)	1.5 (0- 3.77)	0.823[a]
Hospitalization due to N/V	3 (5.7%)	1 (2.1%)	0.619[c]

Data are presented as median (25th-75th percentile) or n (%). PUQE: Pregnancy-unique quantification of emesis, ART: Assisted reproductive technologies, N/V: Nausea/Vomiting. [a]:Mann Whitney U test, [b]: Pearson chi-square test, [c]: Fisher's exact test

significant difference between groups (p=0.397). The median scores of second and third questions were also similar between ART and spontaneous pregnancies (p=0.838 and p=0.204 respectively). Most participants in both groups reported that they never vomited and had 1-2 episodes of retching in a day.

According to the overall PUQE score, 67.9% of patients with ART pregnancies experienced mild NVP while 24.5% had moderate and 7.5% had severe NVP. In the spontaneous pregnancies group, 60.4% experienced mild NVP, 33.3% had moderate NVP and only 6.3% had severe NVP. The overall PUQE score was 5 (3-8.5) in ART pregnancies and 5 (3-10) in spontaneous pregnancies. There was no significant difference regarding NVP severity between spontaneous and ART pregnancies (p=0.650).

As shown in table II, women conceived via ART had gained a median of 2 (0-3) kg while women with spontaneous pregnancies had gained a median of 1.5 (0-3.77) kg after getting pregnant (p=0.823). There was no statistically significant difference regarding hospitalization history due to NVP (p=0.619). One (2.1%) patient required hospitalization due to NVP in the spontaneous pregnancies group whereas 3 (5.3%) patients had hospitalization history in the ART pregnancies group.

Table III shows the logistic regression analyses. Gravida and type of pregnancy (singleton or twin) did not have a statistically significant effect on the severity of NVP.

Discussion

Electrolyte values, weight loss, acetone detection in urine are commonly used tools for evaluating the severity of NVP (12). Some scoring systems have also been proposed to assess the NVP severity objectively. In the present study, we used the validated PUQE scoring system to compare the severity of nausea and vomiting between spontaneous and ART pregnancies. Our results have shown that most ART pregnancies had mild NVP measured with the PUQE scale. ART treatment did not increase severe NVP rates compared to natural conception. Furthermore, weight change during pregnancy and hospitalization rates due to NVP were similar between women conceived with ART and women with natural conception.

Several studies in the literature evaluated the role of assisted reproduction on NVP severity. However, the data presented are rather controversial and there is no general agreement about the effect of ART on NVP. In line with our findings, most studies found no significant difference (13-16). Bordi et al. compared the obstetric outcomes of twin pregnancies conceived with ART and conceived naturally and did not find a significant difference between groups regarding HG (14). In a retrospective cohort study of 4372 ART pregnancies, the percentage of pregnant women who developed HG was 1.7% and the authors concluded that this prevalence was similar to HG prevalence in all pregnant women (17). On the other hand, some studies found ART as a risk factor for HG (18,19). A large retrospective cohort study by Roseboom et al. examined the characteristics of women with HG and found that was HG was more common in women with ART pregnancies (18). In another retrospective study of 437465 pregnant women, Nurmi and colleagues found ART as a risk factor for HG (19). A potential explanation of the controversial results is that there was a great difference in HG definition in these reports. For instance, the study by Roseboom et al. had a low data quality due to the absence of a standardized HG definition. HG group consisted of pregnancies registered as HG by the caregiver (midwife or gynecologist) (18). In the same way, Bordi et al. did not mention HG criteria in their studies (14). Indeed, a previous report analyzing the HG definition used in

Table III: *Evaluation of risk factors associated with Nausea vomiting of pregnancy*

NVP severity[a]		OR (95% CI)	*p*
Moderate NVP	Intercept		0.733
	Gravidity		
	Primigravida	0.57 (0.23-1.39)	0.217
	Multigravida	1.0 (Reference)	
	Type of pregnancy		
	Singleton	0.72 (0.23-2.21)	0.560
	Twin	1.0 (Reference)	
Severe NVP	Intercept		0.068
	Gravidity		
	Primigravida	0.74 (0.15-3.63)	0.710
	Multigravida	1.0 (Reference)	
	Type of pregnancy		
	Singleton	1.17 (0.13-10.85)	0.891
	Twin	1.0 (Reference)	

a:The reference category is 'Mild', NVP: Nausea vomiting of pregnancy, OR: Odds Ratio, CI: Confidence interval

trials showed that there is a substantial variation in HG definition and outcome reporting (20). The author suggested the utilization of a standardized definition. In this sense, the PUQE scale ensures an objective evaluation of NVP and a meaningful comparison of the results of different studies.

In the present study, we evaluated the effect of controlled ovarian stimulation (COS) and fresh embryo transfer cycles on NVP severity. There are various ART protocols such as COS and fresh embryo transfer, natural cycle frozen embryo transfer (FET), and hormone replacement therapy FET cycles. Each protocol creates a distinct hormonal milieu. Therefore, different ART protocols may cause different effects on NVP severity. Importantly, a previous study investigated the effect of different ART techniques on obstetric outcomes and found that conception with ovulation induction and IUI was associated with a reduced risk of HG compared to conception with IVF (14). Therefore, another possible explanation for controversial results between studies may be the ART protocols applied. The protocols were unclear in most studies. Besides, the authors did not mention, if any, the type and route of hormone supplementations administered for luteal phase support (LPS). For instance, in the study by Nurmi et al., the characteristics of ART pregnancies such as multiple or single, ART techniques, and LPS which may affect the outcome, were not specified (19).

Severe NVP can lead to significant weight loss and is the most common reason for hospital admission in early pregnancy (21). In addition to the PUQE scale, we evaluated hospitalization requirements and weight change during pregnancy to assess NVP severity. ART pregnancies had similar rates of hospitalization due to NVP. In addition, weight change during pregnancy was also comparable between groups. These findings also strengthen the results of the PUQE scale suggesting severe NVP does not increase in ART pregnancies.

Although several studies investigated the association of HG with ART, the present study is one of the first studies in the literature evaluating the relationship between ART and NVP severity with a validated scale. The strength of our study is the use of a standardized valid scale for NVP and a clear definition of the ART technique. The main limitation of our study was that groups constituted of both singleton and twin pregnancies. There is a need for studies with more homogeneous groups on the subject.

In conclusion, conception using ART does not increase the severity of NVP and most ART pregnancies have mild NVP similar to naturally conceived pregnancies. In addition, hospital admission rates due to NVP do not increase in ART pregnancies.

Declarations

Ethics approval and consent to participate: This study has been approved by the Institutional Review Board of Kocaeli University, Kocaeli, Turkey (approval number: GOKAEK-2020/1.31 2020/24, approval date: 21.01.2020). All patients gave informed consent to participate in the study. This research was conducted in accordance with the ethical standards of the Helsinki declaration and its later amendments.

Data availability: Derived data supporting the findings of this study are available from the corresponding author on request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: OSYC was responsible for the design of the work, analyzed and interpreted the patient data, and made critical revisions of the manuscript. MD reviewed the literature and was a major contributor in writing the manuscript. All authors read and approved the final manuscript

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