

SEROTONIN SYNDROME AFTER TREATMENT OF NAUSEA AND VOMITING IN PREGNANCY

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ABSTRACT

Background: Nausea and vomiting in pregnancy (NVP) are common and may require ondansetron when first-line measures are inadequate. Although ondansetron is widely used, serotonin syndrome remains a rare but potentially serious adverse event with limited pregnancy-specific evidence.

Objective: To assess the incidence of serotonin syndrome among pregnant women receiving ondansetron for severe NVP and to identify risk factors and clinical outcomes.

Methods: This cross-sectional study included 100 pregnant women aged 18–45 years presenting to the Department of Obstetrics & Gynecology, Ittefaq Trust Hospital, Lahore. Severe NVP was considered a Pregnancy-Unique Quantification of Emesis score of ≥ 13 or when medical intervention was necessary. The sampling technique used was consecutive or non-probability sampling. Serotonin syndrome was determined using the Hunter Serotonin Toxicity Criteria. Data were analysed using SPSS version 26, and chi-square testing was done after stratification, with $p \leq 0.05$ accepted as significant.

Results: Serotonin syndrome was identified in 12.0% of participants. The most common manifestations were tremor, agitation, hyperreflexia, sweating, and autonomic instability. Significant associations were observed with ondansetron dose > 8 mg ($p=0.008$), treatment duration > 5 days ($p=0.001$), BMI ≥ 25 kg/m² ($p=0.014$), gestational age > 12 weeks ($p=0.044$), diabetes mellitus ($p=0.015$), hypertension ($p=0.039$), and anemia ($p=0.022$). No significant associations were found for age, parity, education, residence, occupation, lifestyle, socioeconomic status, and antenatal care.

Conclusion: Serotonin syndrome was a significant number of pregnant women who were undergoing ondansetron therapy for their severe NVP. The dose and the duration of therapy were the most significant associations, which indicated careful clinical monitoring during the therapy in this particular study population.

KEYWORDS: nausea and vomiting in pregnancy; ondansetron; serotonin syndrome; pregnancy; Hunter Serotonin Toxicity Criteria; antiemetic therapy

INTRODUCTION

Nausea and vomiting in pregnancy (NVP) are among the most common symptoms encountered during pregnancy, affecting up to 80% of pregnant women, while approximately 30% may experience symptoms severe enough to require medical intervention [1]. NVP is frequently self-limited, but severe symptoms can significantly affect mothers' quality of life and may result in clinically relevant consequences, such as dehydration, electrolyte disturbances, nutritional deficits, and weight loss [2]. Therefore, effective management of persistent nausea and vomiting is an important aspect of antenatal care, especially if symptoms of nausea and vomiting are impairing daily activities or hospital-based management is required [3].

Because of its proven antiemetic efficacy, ondansetron, a selective serotonin 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist, is commonly used to manage severe NVP. It is now recommended as a second-line pharmacological treatment after pyridoxine and doxylamine, especially in the first trimester, as per the current professional guidance, including recommendations by the American College of Obstetricians and Gynecologists [4]. Continued studies have focused on the maternal and fetal safety of ondansetron in pregnancy, although it certainly has been used widely clinically. Previous investigations have mainly been on the congenital and obstetric outcomes, with controversial results as to the risk of adverse foetal effects, including possible cardiac malformations [5,6].

Serotonin syndrome (SS) is a very rare but potentially lethal clinical syndrome caused by too much serotonin activity in the central nervous system (CNS) [7]. It presents with a variety of neuromuscular, autonomic, and neuropsychiatric features such as agitation, confusion, tremor, hyperreflexia, muscle rigidity, diaphoresis, shivering, and autonomic instability. Most commonly associated with serotonergic drugs such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and some drugs used for migraine, especially when several of these

drugs are used together [6]. Ondansetron is considered generally safe during pregnancy, but it has been suggested that it can help cause serotonin toxicity in susceptible individuals [8].

There is still a lack of evidence specifically concerning the occurrence of serotonin syndrome in pregnant women on Ondansetron for NVP [9]. In a retrospective cohort study, it was reported that pregnant women who were exposed to ondansetron had a slightly increased risk for serotonin syndrome of about 0.1%, but the absolute risk was very low [10]. In general, estimates in the general population taking serotonergic drugs have varied between 0.5 and 0.9 cases per 1,000 patient-years [11]. Additionally, serotonin syndrome has been reported after using these medications for nausea/vomiting in pregnant women, emphasizing the need to recognize this rare side effect. However, the incidence and risk factors for serotonin syndrome in pregnant women treated with ondansetron are poorly understood [12].

In routine clinical practice, management of NVP generally begins with lifestyle modification and first-line pharmacological therapy such as pyridoxine and doxylamine. Treatment with Ondansetron should be reserved for patients who do not have a satisfactory response to these initial measures, taking into account dose and duration of treatment. Since ondansetron is commonly used, this adverse effect warrants further investigation, especially in pregnant women, because of the possibility of serious outcomes from serotonin syndrome. Therefore, the present study aimed to determine the frequency of serotonin syndrome in pregnant women treated with ondansetron for severe nausea and vomiting in pregnancy and to identify associated risk factors and clinical outcomes [13,14].

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional study was conducted in the Department of Obstetrics & Gynecology, Ittefaq Trust Hospital, Lahore, Pakistan. The study duration was 16th January 2026 till 16th June 2026.

Sample Size and Sampling Technique

A sample size of 100 pregnant females was calculated using the WHO sample size calculator, with a 95% confidence level, 10% margin of error, and an assumed frequency of serotonin syndrome of 50% among pregnant females. Participants were recruited using a non-probability consecutive sampling technique.

Inclusion Criteria

Pregnant women aged 18–45 years diagnosed with severe nausea and vomiting in pregnancy, defined as a PUQE score of ≥ 13 or requiring medical intervention, were included. Women using ondansetron for the treatment of NVP, regardless of dose or duration, and having a gestational age of ≤ 20 weeks at the time of enrollment were eligible. Participants were also required to provide informed consent and comply with study procedures.

Exclusion Criteria

Pregnant women with pre-existing psychiatric or neurological disorders that could mimic symptoms of serotonin syndrome, including epilepsy and major depressive disorder, were excluded. Women receiving multiple serotonergic drugs, including selective serotonin reuptake inhibitors or other serotonergic agents known to increase the risk of serotonin syndrome, were also excluded. Additional exclusion criteria included known hypersensitivity or contraindication to ondansetron, chronic medical conditions requiring regular use of medications that could confound study results such as corticosteroids or antiepileptic drugs, multiple pregnancies including twins or triplets, and inability to provide informed consent or participate in follow-up assessments.

Data Collection Procedure

A total of 100 females fulfilling the selection criteria were enrolled from the outpatient department after obtaining informed consent. The following data were collected: Name, age, gestational age, body mass index, parity, education, residence, occupation, lifestyle, prenatal care received, ondansetron used, dose of ondansetron used, and duration of ondansetron therapy received.

After administration of ondansetron, the participants were checked by the researcher for any of the following symptoms: confusion, agitation, muscle twitching, sweating, shivering, diarrhea. Women were deemed to have serotonin syndrome if they exhibited symptoms as per the operational definition. The structured data collection proforma was used in recording all aspects of study-related information.

Ethical Considerations

All participants provided written informed consent, and the study was voluntary. The participants were given details regarding the study, the procedures, potential risks and benefits, confidentiality of their information, and the ability to withdraw from the study at any time without compromising their medical care. The personal identifiers were kept confidential, and the data collected in this study were used only for research. The data obtained from the participants were coded, and only the research team had access to the information. All symptoms suggestive of serotonin syndrome or other clinical concerns during follow-up were treated in the usual manner.

Data Analysis

The collected data have been analyzed with SPSS software version 26. The Shapiro-Wilk test was used to test for normality of quantitative variables. Quantitative variables, including age, gestational age, body mass index, dose of ondansetron, and duration of ondansetron use, were presented as mean and standard deviation.

Qualitative variables like parity, education, occupation, lifestyle, socioeconomic status, diabetes, hypertension, anemia, antenatal care, serotonin use, and serotonin syndrome were presented as frequencies and percentages. Data were stratified based on age, gestational age, BMI, parity, education, residence, occupation, lifestyle, socioeconomic status, diabetes, hypertension, anemia, ANC, ondansetron use, ondansetron dose, and ondansetron duration. The chi-square test was used to compare the groups after stratification in terms of serotonin syndrome. Statistical significance was set at a p-value of ≤ 0.05 .

RESULTS

A total of 100 pregnant women with severe nausea and vomiting in pregnancy who received ondansetron were included in the analysis. The mean age of the participants was 28.7 ± 5.6 years, while the mean gestational age at enrollment was 12.8 ± 3.7 weeks. The mean body mass index was 24.9 ± 3.4 kg/m². Fifty participants (50.0%) were multiparous, 62.0% were urban residents, and 50.0% belonged to the middle socioeconomic group. Diabetes mellitus was present in 12.0%, hypertension in 9.0%, and anemia in 30.0% of participants. Regular antenatal care was reported by 85.0% of the study population. Baseline demographic and clinical characteristics are presented in Table 1.

Table 1. Demographic and Clinical Characteristics of Participants

Variable	Total (n=100)
Age, years	28.7 ± 5.6
Gestational age, weeks	12.8 ± 3.7
BMI, kg/m ²	24.9 ± 3.4
Nulliparous	50 (50.0%)
Multiparous	50 (50.0%)
Education $\leq$ secondary level	55 (55.0%)
Education $>$ secondary level	45 (45.0%)
Urban residence	62 (62.0%)
Rural residence	38 (38.0%)
Employed	28 (28.0%)
Homemaker	72 (72.0%)
Active lifestyle	40 (40.0%)
Sedentary lifestyle	60 (60.0%)
Low socioeconomic status	35 (35.0%)
Middle socioeconomic status	50 (50.0%)
High socioeconomic status	15 (15.0%)
Diabetes mellitus	12 (12.0%)
Hypertension	9 (9.0%)
Anemia	30 (30.0%)
Receiving antenatal care	85 (85.0%)

Values are presented as mean $\pm$ standard deviation or frequency (percentage), as appropriate.

Ondansetron Exposure and Serotonin Syndrome

The mean recorded ondansetron dose was 8.6 ± 3.2 mg, while the mean duration of treatment was 5.4 ± 2.6 days. Serotonin syndrome according to the predefined clinical criteria was identified in 12 participants (12.0%). Among affected participants, tremor was the most frequent manifestation, occurring in 10 patients (83.3%), followed by agitation in 9 (75.0%), hyperreflexia in 8 (66.7%), sweating in 8 (66.7%), and autonomic instability in 7 (58.3%). Confusion and shivering were each observed in 6 patients (50.0%), while muscle rigidity and diarrhea were less frequent. Details of ondansetron exposure and the clinical manifestations of serotonin syndrome are shown in Table 2.

Table 2. Ondansetron Exposure and Clinical Manifestations of Serotonin Syndrome

Variable	Value
Ondansetron dose, mg	8.6 ± 3.2
Duration of ondansetron use, days	5.4 ± 2.6
Serotonin syndrome	12 (12.0%)
Agitation*	9 (75.0%)
Confusion*	6 (50.0%)

Tremor*	10 (83.3%)
Hyperreflexia*	8 (66.7%)
Muscle rigidity*	4 (33.3%)
Autonomic instability*	7 (58.3%)
Sweating*	8 (66.7%)
Shivering*	6 (50.0%)
Diarrhea*	3 (25.0%)

Values are presented as mean $\pm$ standard deviation or frequency (percentage). *Percentages for clinical manifestations are calculated among the 12 participants with serotonin syndrome.

Factors Associated with Serotonin Syndrome

Post-stratification analysis demonstrated that serotonin syndrome occurred more frequently among women with a gestational age >12 weeks, BMI ≥ 25 kg/m², diabetes mellitus, hypertension, anemia, higher ondansetron dose, and longer duration of ondansetron use. Serotonin syndrome was observed in 22.5% of women receiving an ondansetron dose >8 mg compared with 5.0% of those receiving ≤ 8 mg ($p=0.008$). Similarly, the syndrome occurred in 25.0% of participants treated for >5 days compared with 3.3% of those treated for ≤ 5 days ($p=0.001$).

A BMI ≥ 25 kg/m² was associated with a higher frequency of serotonin syndrome compared with BMI <25 kg/m² (22.9% vs 6.2%, $p=0.014$). Significant associations were also observed for gestational age >12 weeks (20.0% vs 6.7%, $p=0.044$), diabetes mellitus (33.3% vs 9.1%, $p=0.015$), hypertension (33.3% vs 9.9%, $p=0.039$), and anemia (23.3% vs 7.1%, $p=0.022$). Age, parity, education, residence, occupation, lifestyle, socioeconomic status, and antenatal care were not significantly associated with serotonin syndrome. These findings are summarized in Table 3.

Table 3. Association of Demographic, Clinical, and Treatment Factors with Serotonin Syndrome

Variable	SS present n (%)	SS absent n (%)	p-value
Age ≥ 30 years	7 (17.5%)	33 (82.5%)	0.167
Age <30 years	5 (8.3%)	55 (91.7%)	
Gestational age >12 weeks	8 (20.0%)	32 (80.0%)	0.044
Gestational age ≤ 12 weeks	4 (6.7%)	56 (93.3%)	
BMI ≥ 25 kg/m ²	8 (22.9%)	27 (77.1%)	0.014
BMI <25 kg/m ²	4 (6.2%)	61 (93.8%)	
Multiparous	9 (18.0%)	41 (82.0%)	0.065
Nulliparous	3 (6.0%)	47 (94.0%)	
Education $\leq$ secondary	8 (14.5%)	47 (85.5%)	0.387
Education $>$ secondary	4 (8.9%)	41 (91.1%)	
Urban residence	7 (11.3%)	55 (88.7%)	0.780
Rural residence	5 (13.2%)	33 (86.8%)	
Employed	3 (10.7%)	25 (89.3%)	0.805
Homemaker	9 (12.5%)	63 (87.5%)	
Active lifestyle	4 (10.0%)	36 (90.0%)	0.615
Sedentary lifestyle	8 (13.3%)	52 (86.7%)	
Diabetes mellitus	4 (33.3%)	8 (66.7%)	0.015
No diabetes mellitus	8 (9.1%)	80 (90.9%)	
Hypertension	3 (33.3%)	6 (66.7%)	0.039
No hypertension	9 (9.9%)	82 (90.1%)	
Anemia	7 (23.3%)	23 (76.7%)	0.022
No anemia	5 (7.1%)	65 (92.9%)	
Antenatal care	10 (11.8%)	75 (88.2%)	0.863
No antenatal care	2 (13.3%)	13 (86.7%)	
Ondansetron dose >8 mg	9 (22.5%)	31 (77.5%)	0.008
Ondansetron dose ≤ 8 mg	3 (5.0%)	57 (95.0%)	
Duration >5 days	10 (25.0%)	30 (75.0%)	0.001
Duration ≤ 5 days	2 (3.3%)	58 (96.7%)	

SS, serotonin syndrome; BMI, body mass index. Associations were assessed using the chi-square test. A p-value ≤ 0.05 was considered statistically significant.

Overall, serotonin syndrome was identified in 12.0% of pregnant women treated with ondansetron for severe nausea and vomiting in pregnancy. Higher ondansetron dose and longer duration of therapy showed the strongest associations

with serotonin syndrome, while elevated BMI, later gestational age, diabetes mellitus, hypertension, and anemia were also significantly associated with its occurrence. No statistically significant association was observed with age, parity, education, residence, occupation, lifestyle, socioeconomic status, or antenatal care.

DISCUSSION

The present study evaluated serotonin syndrome among pregnant women receiving ondansetron for severe nausea and vomiting in pregnancy [1]. Serotonin syndrome was identified in 12.0% of participants, and its occurrence was significantly associated with higher ondansetron dose, longer duration of treatment, higher body mass index, gestational age beyond 12 weeks, diabetes mellitus, hypertension, and anemia. Among treatment-related factors, an ondansetron dose >8 mg and treatment duration >5 days demonstrated particularly strong associations with serotonin syndrome. In contrast, age, parity, education, residence, occupation, lifestyle, socioeconomic status, and antenatal care were not significantly associated with the outcome [2,3].

Nausea and vomiting are frequent during pregnancy and may substantially impair maternal well-being when symptoms become severe [1,2]. Ondansetron is commonly used when initial measures and first-line pharmacological therapies fail to provide adequate symptom control [4]. Although much of the available literature regarding ondansetron in pregnancy has concentrated on fetal and obstetric safety, comparatively little attention has been given to serotonin syndrome as a potential adverse clinical event [5]. The present findings therefore address an area in which available pregnancy-specific evidence remains limited [6].

The observed frequency of serotonin syndrome in this study was higher than that reported in some previous literature. Sakran et al. reported a substantially lower absolute occurrence among pregnant women exposed to ondansetron [7]. Similarly, serotonin syndrome remains uncommon in broader populations receiving serotonergic medications, with previously reported incidence estimates considerably lower than the frequency observed in the present study [8]. Differences in study populations, clinical characteristics, case identification methods, severity of NVP, treatment exposure, and surveillance for neurological and autonomic manifestations may contribute to differences between studies. The current study specifically evaluated women with severe NVP receiving ondansetron and actively assessed manifestations compatible with serotonin toxicity, which may have facilitated recognition of symptomatic cases [9]. Among the affected participants, the clinical manifestations were mostly neuromuscular and autonomic. The most common symptoms were tremor, agitation, hyperreflexia, sweating, confusion, and shivering [10]. This clinical pattern is seen in serotonin syndrome, which is a recognized syndrome of altered mental status, autonomic dysfunction, and neuromuscular hyperactivity [5, 6]. Past studies reporting serotonin syndrome after pharmacologic therapy for nausea/vomiting in pregnancy add to the need for awareness of such complications in obstetric patients [9]. Importantly, this is clinically relevant, as signs and symptoms of agitation, tremor, diaphoresis, or gastrointestinal symptoms may be mistaken for pregnancy, dehydration, anxiety, or severity of NVP itself [10,11].

One interesting observation was the link between exposure parameters and the occurrence of serotonin syndrome with ondansetron [12]. The incidence of serotonin syndrome was higher in women receiving doses >8 mg than in women receiving doses ≤8 mg and was higher with treatment durations >5 days. These findings have clinical implications for the intensity and duration of treatment that will be seen in women receiving ondansetron. But as this is a cross-sectional study, these associations should be considered as relationships rather than causal effects [13,14].

Higher BMI was also found to be significantly associated with serotonin syndrome. Furthermore, women with diabetes mellitus (DM), hypertension (HT), and anemia (AN) showed higher rates of the syndrome. These data could suggest that maternal clinical factors contribute to the vulnerability of adverse presentation throughout therapy [13]. However, because the study was focused on evaluating the frequency and stratified associations, these findings should not be interpreted as independent causal predictors without further analytical investigation [15].

There was no significant relationship between maternal age or parity and the frequency of serotonin syndrome, but gestational age >12 weeks was. Likewise, no significant associations were detected for education, residence, occupation, lifestyle, socioeconomic status, or antenatal care. This trend indicates that variables related to treatment and clinical aspects may be more important than general sociodemographic variables in this study population for the development of serotonin syndrome [16].

The results are of practical significance for the treatment of severe NVP. Ondansetron is important in the treatment scheme, especially when first-line treatment fails, but should be considered for neurological, autonomic, and behavioral signs and symptoms suggestive of serotonin toxicity in women who are taking it [16,17]. Special consideration might be indicated for patients receiving higher doses or longer treatment courses, and in patients with underlying metabolic or clinical abnormalities. These results should not be viewed as a reason not to use ondansetron appropriately, but rather should be seen as a reason to be careful in the clinical assessment and monitoring of patients while on ondansetron [18].

Several limitations should be considered. The study was done at one institution with 100 participants, using non-probability consecutive sampling, which may affect the generalizability of the results. The cross-sectional study design limits the ability to assess temporal and causal relationships. Further, the number of subjects with serotonin syndrome

is relatively small, and it is difficult to analyze the results for this subgroup in detail. However, these pre-established definitions of severe NVP and clinical assessment of serotonin syndrome seemed to offer a systematic way of examining an unusual and possibly serious adverse event in this patient population [19,20].

CONCLUSION

Serotonin syndrome was detected in 12.0% of all pregnant women treated for SVEP with ondansetron. Occurrence was significantly associated with higher dose of ondansetron, longer treatment duration, higher BMI, gestational age >12 wks, diabetes mellitus, hypertension and anemia. Treatment factors, especially dose of ondansetron > 8 mg and days of treatment >5, were most strongly associated. Neurological, autonomic and behavioral signs of serotonin syndrome should therefore be kept in mind and monitored carefully in pregnant women receiving ondansetron for severe NVP. These associations need to be confirmed with more subjects, and clinically associated risk factors need to be better characterized.

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Authors' Contributions

BJ: Conceptualization, data collection, methodology, data analysis, manuscript preparation, and final approval.

MZ: Supervision, study design, clinical oversight, critical review, and final approval.

MS: clinical assessment, interpretation of findings, manuscript review, and final approval.

H: Clinical input, methodology, interpretation of findings, critical review, and final approval. All authors read and approved the final manuscript and agreed to be accountable for the work.

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