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**ORIGINAL ARTICLE**

# Comparison of Ondansetron with Doxylamine plus Pyridoxine for the Treatment of Nausea and Vomiting during Pregnancy

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## ABSTRACT

**Introduction:** Nausea and vomiting in pregnancy (NVP) impacts up to 80% of pregnant women and can considerably diminish quality of life. Despite the endorsement of doxylamine and pyridoxine as first-line treatment, a significant proportion of women encounter insufficient symptom management or unpleasant reactions. Ondansetron has surfaced as a plausible option; yet, comparison data are still few, especially in outpatient contexts.

**Objective:** To evaluate the effectiveness and safety of oral ondansetron against doxylamine combined with pyridoxine in the management of moderate to severe nausea and vomiting in pregnancy (NVP).

**Materials and Methods:** This randomized controlled experiment was performed in Mother & Child Healthcare Center (MCHC), Pakistan Institute of Medical Sciences, Islamabad from June 4, 2021 to December 4, 2021. One hundred twenty-six pregnant women with a gestational age of less than 16 weeks and a PUQE score exceeding 6 were randomized into two groups. Group A was administered oral ondansetron, whereas Group B was given doxylamine in conjunction with pyridoxine for a duration of five days. The severity of symptoms was evaluated using the PUQE score at baseline and on day five.

**Results:** The baseline features were similar among the groups. Ondansetron produced a much bigger decrease in PUQE ratings and a higher percentage of patients attaining ≥50% symptom relief in comparison to doxylamine–pyridoxine. The adverse effects were minor and similar across the groups.

**Conclusion**: In conclusion, oral ondansetron demonstrates superior efficacy compared to: doxylamine + pyridoxine in managing moderate to severe nausea and vomiting in pregnancy, while maintaining a comparable safety profile.

**Keywords:** Nausea and vomiting in pregnancy, ondansetron, doxylamine, pyridoxine, PUQE score

## INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is a medical ailment that is highly prevalent among pregnant women, especially in the first trimester of pregnancy, they are almost universal in nearly 70 80% across the world. Most women with the condition develop mild to moderate symptoms, although a subgroup develops hyperemesis gravidarum (HG), a severe form of the condition, which is characterized by dehydration, electrolyte imbalance, weight loss, and high maternal morbidity[1,2]. The symptoms normally appear at 4-6 gestational weeks, climax at 8-12 gestational weeks, and normally disappear at 20 gestational weeks though in some women it continues all the way to pregnancy with negative impact on physical, psychological and social comfort.

NVP is based on management by the severity of the symptoms and aims at alleviating the symptoms without compromising the safety of the mother and fetus. The combination of doxylamine and pyridoxine as the primary pharmacotherapy is suggested by international standards, such as RCOG or those of Canadian authorities, because it is safe and economical[3]. Nevertheless, women are still having a significant percentage of persistent nausea and vomiting, diminished quality of life, sedation, and dizziness, causing discontinuation of treatment, polypharmacy, and hospitalization. Ondansetron, a well-known antiemetic in non-pregnant patients, has demonstrated helpful outcomes with lower sedative side effects, and recently, there is changeable information that Ondansetron could work as well as or better than doxylamine as pyridoxine in managing the symptoms of NVP[4,5].

NVP in Pakistan is not well-recognized and not well-treated because of the limited awareness of the condition and fear of using medications during pregnancy and the absence of evidence produced locally to inform clinical practice[6]. The fluctuation of healthcare access, use of empirical treatment, and the lack of uniform techniques of assessment like PUQE scoring make it even more difficult to manage[7]. The vast majority of treatment regimens are based on extrapolated data, which is not necessarily well representative of the local patient population, health care environment, and socioeconomic characteristics, and so, it should be replaced with a context-specific study.

**Significance:** Though foreign literature indicates better or equal efficacy of ondansetron over doxylamine-pyridoxine, there is no literature that directly compares these two agents in NVP and there is also a paucity of local information on South Asian or Pakistani population. The assessment of ondansetron as an alternative first or second line treatment could assist in ensuring the optimal control of symptoms, decreased adverse effects, and enhanced quality of life among pregnant women. Production of local evidence is essential to support the clinical guidelines, minimize unnecessary hospitalization effects, and patient concerns about safety and effectiveness.

**Objective:** To compare the efficacy of the ondansetron and doxylamine plus pyridoxine for treating vomiting and nausea up to 16 weeks gestational age.

## MATERIALS AND METHODS

**Study Setting and Duration:** This was a randomized controlled trial that was conducted in the Department of Gynecology and Obstetrics, Mother & Child Healthcare Center (MCHC), Pakistan Institute of Medical Sciences, Islamabad. The research was conducted within a 6 months time frame from June 4, 2021 to December 4, 2021 after the study synopsis was approved by the institutional ethics committee.

**Study Design and Sample Size:** The type of design used was a randomized controlled trial. The sample size is calculated with the help of WHO sample size calculator. This was calculated using the level of significance of 5% and power of 80 with population standard deviation at 0.2. The value of the population mean PUQE score using ondansetron was 6.5 and the expected population mean PUQE score using doxylamine plus pyridoxine was 6.6. According to these parameters, there was a need to include 63 patients in each group thus the overall sample size was 126 participants.

**Sampling Technique and Selecting the sample:** The eligible participants were recruited by non-probability consecutive sampling.

Pregnant women with nausea and vomiting secondary to pregnancy were studied when they had moderate and severe symptoms as characterized by a PUQE score of more than 6 and less than 16 weeks of gestational age proved through ultrasonography.

Women were left out when they had nausea or vomiting before pregnancy, were hospitalized with NVP during pregnancy, had been known to be hypersensitive to any study medication, or could not come back to a follow-up visit or could not be contacted by telephone within 1 week.

**Data Collection Procedure:** The hospital ethics committee gave his consent to the study before enrollment of patients. The Gynecology and Obstetrics Department of MCH, PIMS, Islamabad recruited pregnant women with gestational age less than 16 weeks presenting with the complaint of nausea and vomiting and satisfying inclusion criteria. All the participants were provided with written informed consent.

An elaborate medical history was conducted in order to rule out predisposing or precipitating conditions as well as systemic diseases that might complicate the medical treatment to be received. Full physical examination was done. All participants were subjected to baseline laboratory tests according to unit protocol, such as blood grouping, complete blood count, tests of renal functioning, liver functioning, and routine urine analysis.

The lottery approach was applied to assign the participants into two groups randomly. Ondansetron was administered to Group A and a mixture of doxylamine and pyridoxine was applied in Group B. Baseline PUQE scores were taken before the treatment was initiated. Group A patients received 4mg of ondansetron orally at a 5-day dose of 4 mg every 8 hours. Group B patients were given a combination pill that consisted of doxylamine 10mg and pyridoxine 10mg, every 8 hours, over five days. Every participant was advised on the adherence of medication.

On the fifth day of treatment, the follow-up was done. Patients failing to attend physically were conducted on telephone follow-up. The PUQE scores were reevaluated on day five and the difference between the baseline and post-treatment scores was determined. A clinical significance of 50% or greater reduction in PUQE score was defined and each group was registered. Adverse effects were also asked, and, in this case, recorded by the participants. To achieve the accuracy of the data and adherence to protocols, all the data were taken by the principal investigator and documented on a predesigned pro forma.

**Data Analysis Procedure:** The data analysis and entry were carried out using SPSS version 23. Using the means and standard deviation, quantitative variables, such as the maternal age, gestational age, BMI, baseline PUQE score, and PUQE score at day five, were represented. Qualitative variables (the rate of patients who attained the 50% reduction of PUQE score, and the phenomenon of side effects) were reported as frequencies and percentages.

The chi-square test or Fisher exact test was used where necessary to compare the proportion of patients who experienced 50 percent or more reduction of PUQE score between the two groups. The controlled variables were potential effect modifiers, such as age, gestational age, and BMI. Chi-square or Fisher exact test was employed in order to perform post-stratification analysis. The p-value was taken to be significant at =.05.

## RESULTS

A total of 126 pregnant women were enrolled, with equal distribution across the ondansetron and doxylamine–pyridoxine groups. The two groups exhibited comparability for mean mother age and age-group distribution, revealing no statistically significant difference. Gravidity was comparable throughout the groups. A notably greater percentage of women in the ondansetron group were beyond 8 weeks of gestation compared to the doxylamine–pyridoxine group (p = 0.034). The ondansetron group had a considerably reduced parity (p = 0.006), although all other baseline obstetric characteristics were equivalent, suggesting overall baseline equivalence between the groups.

Anthropometric data, such as weight, height, and body mass index, were comparable in both treatment groups at enrollment. No statistically significant difference was seen in mean BMI or the distribution of BMI categories (<25 kg/m² and ≥25 kg/m²) between the ondansetron and doxylamine–pyridoxine groups, indicating that body habitus was comparable at baseline and unlikely to influence treatment effects.

Table 1: Baseline Demographic and Obstetric Characteristics of Study Participants

| Variable | Group A (Ondansetron) n=63 | Group B (Doxylamine–Pyridoxine) n=63 | p-value |
|---|---|---|---|
| Age (years), mean ± SD | 27.06 ± 4.91 | 26.48 ± 5.35 | 0.522 |
| Age group | | | 0.590 |
| ≤25 years, n (%) | 26 (41.3) | 29 (46.0) | |
| >25 years, n (%) | 37 (58.7) | 34 (54.0) | |
| Gestational age | | | 0.034 |
| ≤8 weeks, n (%) | 14 (22.2) | 25 (39.7) | |
| >8 weeks, n (%) | 49 (77.8) | 38 (60.3) | |
| Gravida, mean ± SD | 2.40 ± 0.61 | 2.43 ± 0.56 | 0.761 |
| Para, mean ± SD | 1.48 ± 0.50 | 1.71 ± 0.46 | 0.006 |

Table 2: Anthropometric Characteristics of Study Participants

| Variable | Group A (Ondansetron) n=63 | Group B (Doxylamine–Pyridoxine) n=63 | p-value |
|---|---|---|---|
| Weight (kg), mean ± SD | 69.37 ± 9.81 | 69.02 ± 9.37 | 0.839 |
| Height (cm), mean ± SD | 159.02 ± 2.45 | 158.90 ± 2.59 | 0.805 |
| BMI (kg/m²), mean ± SD | 24.67 ± 2.43 | 24.70 ± 2.53 | 0.943 |
| BMI category | | | 0.716 |
| <25 kg/m², n (%) | 37 (58.7) | 39 (61.9) | |
| ≥25 kg/m², n (%) | 26 (41.3) | 24 (38.1) | |

Table 3: Comparison of PUQE Scores Between Study Groups

| PUQE Score | Group A (Ondansetron) n=63 | Group B (Doxylamine–Pyridoxine) n=63 | p-value |
|---|---|---|---|
| Baseline (Day 1), mean ± SD | 10.67 ± 1.98 | 10.97 ± 1.99 | 0.395 |
| Day 5 post-treatment, mean ± SD | 5.19 ± 1.51 | 6.57 ± 1.17 | <0.001 |
| Mean reduction in PUQE score | 5.38 ± 1.18 | 4.22 ± 1.11 | <0.001 |

Table 4: Treatment Efficacy and Adverse Effects

| Treatment Efficacy | Efficacy (≥50% PUQE reduction) | Group A n (%) | Group B n (%) | p-value |
|---|---|---|---|---|
| | Present | 48 (76.2) | 37 (58.7) | 0.036 |
| | Absent | 15 (23.8) | 26 (41.3) | |
| Adverse Effects | Adverse Effect | Group A n (%) | Group B n (%) | p-value |
| | Headache | 4 (6.3) | 6 (9.5) | |
| | Dizziness | 6 | 9 | |
| | Fatigue | 11 (17.5) | 4 (6.3) | |
| | Back pain | 10 (15.9) | 5 (7.9) | |
| | Dry mouth | 5 (7.9) | 12 (19.0) | |
| | GI disturbances | 9 (14.3) | 7 (11.1) | |
| | Abdominal pain | 9 (14.3) | 10 (15.9) | |
| | Constipation | 6 (9.5) | 13 (20.6) | |
| | Overall comparison | | | 0.111 |

Table 5: Stratified Analysis of Treatment Efficacy

| Stratification Variable | Category | Group A Efficacy n (%) | Group B Efficacy n (%) | p-value |
|---|---|---|---|---|
| Age (years) | ≤25 | 20/26 (76.9) | 19/29 (65.5) | 0.384 |
| | >25 | 28/37 (75.7) | 18/34 (52.9) | 0.052 |
| Gestational age | ≤8 weeks | 10/14 (71.4) | 17/25 (68.0) | 1.00 |
| | >8 weeks | 38/49 (77.6) | 20/38 (52.6) | 0.021 |
| BMI (kg/m²) | <25 | 27/37 (73.0) | 22/39 (56.4) | 0.156 |
| | ≥25 | 21/26 (80.8) | 15/24 (62.5) | 0.211 |

The baseline severity of nausea and vomiting, assessed by the PUQE score on day 1, was analogous across the two groups, signifying an equivalent start symptom load. After five days of therapy, the ondansetron group had a markedly lower PUQE score than the doxylamine–pyridoxine group ($p < 0.001$). The average decrease in PUQE score from baseline was considerably higher in patients administered ondansetron, indicating enhanced symptom management throughout the treatment duration.

Treatment efficacy, defined as a ≥50% reduction in PUQE score, was achieved in a significantly higher proportion of patients treated with ondansetron compared to those receiving doxylamine–pyridoxine ($p = 0.036$). Both treatment regimens were generally well tolerated. The frequency and distribution of reported adverse effects did not differ significantly between the two groups ($p = 0.111$), indicating comparable safety profiles.

Stratified analysis indicated that maternal age and BMI did not significantly affect treatment effectiveness in either cohort. Gestational age influenced the results, as ondansetron exhibited much increased effectiveness in women with a gestational age beyond 8 weeks ($p = 0.021$). No substantial difference in effectiveness was noted between treatment groups in women with a gestational age of 8 weeks or less.

## DISCUSSION

Nausea and vomiting in pregnancy (NVP) affects up to 70–80% of pregnant women and, in nearly one- third of cases, causes significant physical discomfort, psychological, and socioeconomic burden as a result of diminished work productivity and high healthcare use[8,9]. Although this condition is often considered to be benign, moderate to severe NVP can significantly affect the quality of life of the mother and can affect pregnancy outcomes in a negative way under such circumstances, unless properly treated. Thus, finding efficient, secure, and feasible treatment alternatives is a pivotal point of obstetric treatment.

Ondansetron has been proven to be an efficient antiemetic in chemotherapy-related, radiation-related, and postoperative nausea and vomiting where it has been shown to have high effectiveness as compared to traditional agents. Nevertheless, there is limited evidence comparing ondansetron and doxylamine-pyridoxine in the treatment of NVP especially in an oral form that can be used in the outpatient setting. A number of earlier trials used ondansetron intravenously, or had small samples, which restricted applicability [10,11]. The current research paper took this gap by conducting its assessment of oral ondansetron and head to head comparison with the conventional first-line combination of doxylamine and pyridoxine.

The results of the current study showed that ondansetron was of a much better symptom relief than at doyxlamine-pyridoxine based on a higher reduction in PUQE scores and higher rate of patients with a clinical meaningful improvement. These findings are similar to those found by previous studies who also found that ondansetron was better at managing nausea and vomiting in pregnancy [12,13]. This increased potency of ondansetron is biologically possible, since it is selective in antagonizing 5-HT3 receptors both in the central chemoreceptor trigger region and the gastrointestinal tract, giving rise to a stronger inhibitory effect on the emetic system than the histaminergic and vestibular systems that are the targets of doxylamine.

The issue of safety is also a significant concern when prescribing drugs during pregnancy. The frequency and the nature of adverse effects in the present study showed similarity between the two treatment groups wherein there was no statistically significant difference. These results are in line with previous studies that indicate that ondansetron and doxylamine-pyridoxine are broadly well tolerated during pregnancy[14]. No significant increase in the number of congenital anomalies or severe fetal adverse outcomes of either regimen had been reported before, which is further evidence that they are relatively safe when used correctly.

NVP management is not just important in controlling maternal symptoms. Previous researchers showed that severe NVP is linked to poor perinatal outcomes such as low weight and preterm birth. Better management of nausea and vomiting can thus help to provide better maternal nutrition, hydration, and health of pregnancy[9,15]. In spite of the low cost of doxylamine-pyridoxine, ondansetron could be more cost-effective in the long-run because it can be used to produce faster and more lasting symptom relief, and, as a result, fewer frequent visits to the clinic, changes in the medication prescription, and hospitalizations.

**Strengths and limitations:** The positive aspects of the given study are its random and controlled nature, sufficient sample size, application of a proven symptom severity scale (PUQE score), and testing of an oral ondansetron regimen that could be used in the outpatient setting. There are however a few limitations that need to be mentioned. This implies that the research was done in one center, which could be a limitation of generalizability. There was no assessment of fetal outcomes and long-term maternal outcomes and follow-up that was confined to five days. Also, there was no use of blinding, and this can create a response bias.

## CONCLUSION

The baseline demographic, obstetric, and anthropometric characteristics were largely comparable between the study groups. Ondansetron demonstrated significantly greater improvement in PUQE scores, higher overall treatment efficacy, and comparable safety relative to doxylamine–pyridoxine. Stratified analysis indicated that the superior efficacy of ondansetron was particularly evident beyond eight weeks of gestation, while age and BMI did not significantly influence treatment response. Collectively, these findings suggest that oral ondansetron is a more effective therapeutic option than doxylamine plus pyridoxine for the management of moderate to severe nausea and vomiting in pregnancy, with a similar side-effect profile.

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