Pyridoxine for nausea and vomiting of pregnancy: A randomized, double-blind, placebo-controlled trial

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OBJECTIVE: Our purpose was to determine the effectiveness of pyridoxine for nausea and vomiting of pregnancy.
STUDY DESIGN: During an 11-month period 342 women who first attended Chiang Mai University Hospital antenatal clinic at ≤17 weeks' gestation were randomized to receive either oral pyridoxine hydrochloride, 30 mg per day, or placebo in a double-blind fashion. Patients graded the severity of their nausea by a visual analog scale and recorded the number of vomiting episodes over the previous 24 hours before treatment and again during 5 consecutive days on treatment.
RESULTS: There was a significant decrease in the mean of posttherapy minus baseline nausea scores in the pyridoxine compared with that in the placebo group (*t* test, $p = 0.0008$). There was also a greater reduction in the mean number of vomiting episodes, but the difference did not reach statistical significance ($p = 0.0552$).
CONCLUSION: Pyridoxine is effective in relieving the severity of nausea in early pregnancy. (Am J Obstet Gynecol 1995;173:881-4.)

Key words: Nausea and vomiting of pregnancy, pyridoxine hydrochloride, randomized trial

Nausea in early pregnancy is so common that it has been accepted as presumptive evidence of pregnancy.[1] Various treatments have been empirically recommended for this disorder, reflecting the many theories as to its cause.[2] There is evidence from many case series[3-5] and at least from one randomized trial[6] that pyridoxine (vitamin B_6) may be effective in this regard. Unfortunately, the only trial for pyridoxine[6] was too small to show treatment effects in patients with mild to moderate nausea during the 3-day study. The purpose of the current study was to evaluate the effectiveness of pyridoxine in a larger group of subjects over a longer period, 5 days.

Material and methods

The study was approved by the ethical committee of the Faculty of Medicine, Chiang Mai University. Subjects were recruited from the antenatal clinic at Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University, in Thailand. We included only pregnant women with nausea of pregnancy, with or without vomiting, who first attended the clinic at gestational age ≤17 weeks. We excluded pregnant women who (1) had other medical disorders such as hepatitis or gastrointestinal diseases that might manifest with nausea or vomiting, (2) were mentally retarded or had language or geographic barriers, (3) had taken other medications in the past week that might aggravate or alleviate nausea or vomiting, such as iron tablets, antiemetics, etc., (4) were unable to take the medication as prescribed, or (5) were unable to return for a follow-up visit within 1 week. All patients meeting eligibility requirements were informed of the purpose and the method of the study and were invited to participate. After informed consent was obtained, patients underwent a general physical examination and a routine obstetric evaluation. Patients were then randomized into two groups by a table of random numbers. Those in the pyridoxine (vitamin B_6) group received 20 10-mg tablets of pyridoxine hydrochloride to be taken orally every 8 hours. They were advised to take the medication between 6 and 8 AM, 2 to 4 PM, and 10 to 12 PM for 5 days. Patients in the placebo group received identical-looking tablets in the same regimen. Pyridoxine and the placebo tablets were prepared by the hospital pharmacy and were packed similarly in an envelope containing 20 tablets each. Neither the physicians nor the patients knew the identity of the tablet administered. A list that revealed drug codes was kept by the research assistant and was not accessible to the physicians. Patients in both groups were advised to divide their meals into frequent small ones rich in carbohydrates and low

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Table I. Baseline characteristics of patients

	Placebo (n = 167)	*Pyridoxine (n = 169)*
Age (yr)	27.1 ± 5.4	26.9 ± 5.2
Parity		
Primiparous	84 (50.3%)	80 (47.3%)
Multiparous	83 (49.7%)	89 (52.7%)
Gestational age (wk)	10.9 ± 2.8	10.9 ± 2.7
Duration of nausea (wk)	3.9 ± 2.7	3.8 ± 2.4
Baseline nausea scores (cm)	4.9 ± 2.4	5.2 ± 5.3
Episodes of vomiting in previous 24 hr	1.6 ± 2.0	1.8 ± 2.3
Education		
None	1 (0.6%)	1 (0.6%)
Primary school	129 (77.2%)	129 (76.3%)
Secondary school	26 (15.6%)	28 (16.6%)
University	11 (6.6%)	11 (6.5%)
Occupation		
Employee	70 (41.9%)	81 (47.9%)
Dressmaker	12 (7.2%)	13 (7.7%)
Merchant	23 (13.8%)	20 (11.8%)
Housewife	24 (14.4%)	30 (17.8%)
Agricultural	31 (18.5%)	19 (11.2%)
Civil servant	7 (4.2%)	6 (3.6%)

Data are presented as mean ± SD or number and percent.

in fat. They were also advised not to take any other medications.

Patients were asked to grade the severity of nausea on the visual analog scale. They rated symptoms by marking "X" on the vertical line (10 cm in length) ranging from 0 = no nausea and 10 = nausea as bad as it could be, corresponding to their perceived states. The first record was made on the initial visit to reflect the severity of nausea over the past 24 hours. On the following 5 days recordings of the severity of nausea were made twice daily (i.e., at noon and at bedtime). Patients were also requested to record the number of episodes of vomiting over the last 24 hours before the initial visit and also on each subsequent day of treatment. Patients were requested to return in 1 week to assess their responses to treatment. Those who did not return were contacted by telephone or mail. Compliance was assessed by pill count and by monitoring attendance at scheduled visits.

In this study the primary outcome was the change in the severity of nausea, which is a subjective measure. To obtain an objective measurement, we measured the markings on each of the visual analog scales in centimeters. Next we calculated the average daily nausea scores and the mean nausea score over the 5 days of treatment for each subject. The change in the severity of nausea for each subject was then obtained by subtracting the mean nausea score from the corresponding baseline nausea score. Finally, we compared the mean change in the severity of nausea (posttherapy minus baseline nausea scores) in the pyridoxine and placebo groups by the independent t test. A secondary outcome was the change in the number of vomiting episodes in the two groups, which were again compared by t test. The proportions of subjects with vomiting before and after treatment were also compared by χ^2 tests. We considered the result significant at a value of $p < 0.05$.

Table II. Mean difference in nausea scores in placebo and pyridoxine groups

Group	*No.*	*Mean change in nausea scores (baseline − posttherapy)*	*Significance*
Day 1			
Placebo	167	1.2 ± 2.4	$p = 0.0001$
Pyridoxine	169	2.2 ± 2.1	
Day 2			
Placebo	167	1.7 ± 2.8	$p = 0.0002$
Pyridoxine	169	2.8 ± 2.3	
Day 3			
Placebo	166	2.1 ± 3.0	$p = 0.0011$
Pyridoxine	168	3.0 ± 2.4	
Day 4			
Placebo	165	2.5 ± 3.2	$p = 0.0282$
Pyridoxine	168	3.2 ± 2.6	
Day 5			
Placebo	165	2.7 ± 2.9	$p = 0.0421$
Pyridoxine	168	3.3 ± 2.7	
Mean			
Placebo	167	2.0 ± 2.7	$p = 0.0008$
Pyridoxine	169	2.9 ± 2.2	

Results

Of 3321 pregnant women who first attended the antenatal clinic at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University between May 24, 1993, and April 1, 1994, only 342 met the eligibility criteria and consented to participate in the study. Of these, 169 were assigned to the placebo and 173 to the pyridoxine group. Two patients in the placebo (1.2%) and four in the pyridoxine group (2.4%) did not return for follow-up visits and were excluded, leaving 336 patients in the study. There was no statistically significant difference in baseline characteristics of the two groups (Table I).

On follow-up visits one patient in each group did not rate her nausea scores on treatment day 3, whereas two in the placebo and one in the pyridoxine group did not record their scores on both days 4 and 5 of treatment. The mean change in nausea scores (baseline minus average posttherapy nausea scores for all subjects) in the pyridoxine group was significantly greater ($p = 0.0008$) than those in the placebo group (Table II).

One hundred eleven women of 169 (65.7%) in the pyridoxine group and 108 of 167 (64.7%) in the placebo group had one or more vomiting episodes during the 24 hours before treatment (Pearson χ^2 0.038, $p = 0.8640$). After 5 days of treatment the proportions of women who had vomiting (61/168 in the pyridoxine vs 56/165 in the placebo group [three cases had missing data]) were not statistically different (Pearson χ^2 0.205, $p = 0.6506$). When we obtained the average number of vomiting episodes over the 5 days of treatment and

subtracted this from the corresponding baseline value for each patient and then calculated the overall mean change in the number of vomiting episodes for subjects in the pyridoxine and the placebo groups, we found that there was a greater reduction in the number of vomiting episodes in the pyridoxine than in the placebo group. However, the difference did not reach statistical significance ($p = 0.0552$) (Table III).

There was also no statistically significant difference ($p = 0.2770$) in the proportions of patients who said they had followed the advice to divide their meals into frequent small ones rich in carbohydrates and low in fat (91/167 or 54.5% in the placebo group vs 102/169 or 60.4% in the pyridoxine group). Compliance, as assessed by pill count, revealed that 139 of 167 patients (83.2%) in the placebo group took at least 15 of the 20 prescribed tablets, compared with 141 of 169 (83.4%) in the pyridoxine group. Two patients in the placebo group (1.2%) and four in the pyridoxine group (2.4%) did not return for follow-up visits. Of those who returned, four in the placebo group and five in the pyridoxine group were late for their scheduled appointments.

Table III. Mean change in number of vomiting episodes in placebo and the vitamin B_6 (pyridoxine) groups

Group	*No.*	*Mean change in No. of vomiting episodes (baseline − posttherapy)*	*Significance*
Day 1			
Placebo	111	0.07 ± 2.5	$p = 0.0469$
Pyridoxine	112	0.67 ± 1.9	
Day 2			
Placebo	111	0.32 ± 3.0	$p = 0.0142$
Pyridoxine	112	1.17 ± 2.1	
Day 3			
Placebo	110	0.64 ± 2.9	$p = 0.0237$
Pyridoxine	111	1.42 ± 2.1	
Day 4			
Placebo	109	1.15 ± 2.3	$p = 0.1537$
Pyridoxine	111	1.59 ± 2.2	
Day 5			
Placebo	109	1.34 ± 2.3	$p = 0.7594$
Pyridoxine	111	1.44 ± 2.6	
Average			
Placebo	111	0.65 ± 2.4	$p = 0.0552$
Pyridoxine	112	1.22 ± 2.0	

Comment

In spite of considerable research the cause of nausea and vomiting in early pregnancy remains unknown, and it is possible that more than one mechanism may be involved.[7] Given that this condition is self-limited, it is not surprising that uncontrolled trials of various treatments have yielded rather impressive results.[8]

The same holds true for pyridoxine, which has been empirically recommended for nausea of pregnancy for >40 years.[3-5] Pyridoxine was included in the formulation of Debendox (United Kingdom), which was previously marketed as Bendectin in the United States by Merrell Dow Pharmaceuticals (Cincinnati). Bendectin was the only drug approved by the United States Food and Drug Administration for the treatment of nausea during pregnancy.[8, 9] Originally the drug contained the antispasmodic agent dicyclomine hydrochloride, 10 mg, the antihistamine doxylamine, 10 mg, and pyridoxine hydrochloride, 10 mg. Later dicyclomine was dropped from the United States formulation because placebo-controlled trials showed that the component by itself had no significant therapeutic effect.[9] According to the Cochrane database of perinatal trials,[8] there have been only three controlled trials of Debendox. The overview of these three trials gives strong evidence that Debendox provides considerable relief for nausea and vomiting in pregnancy (typical odds ratio 0.3, 95% confidence interval 0.16 to 0.54). The remaining question is which of the two components of Debendox, doxylamine or pyridoxine (vitamin B_6) or both, is the active ingredient. This is more than just academic curiosity, because some recent studies[10, 11] raise the concern that doxylamine may be teratogenic. On the contrary, the available evidence does not suggest a teratogenic risk from the ingestion of pyridoxine during pregnancy.[12]

To our knowledge, there has been only one randomized, double-blind, placebo-controlled trial of pyridoxine for the treatment of nausea and vomiting in pregnancy in the English literature. In that study Sahakian et al.[6] reported a significant reduction in mean nausea scores in a subgroup of patients with severe nausea who received pyridoxine compared with that in the placebo group ($p < 0.01$). However, they did not find a significant difference between the treatment and placebo in patients with mild to moderate nausea and in the group as a whole. To show such treatment effect with a probability of a type I error of 5% (two-tailed) and a probability of a type II error of 20% (i.e., a power of 80%), they needed to recruit ≥300 patients. Unfortunately, the study included only 74 subjects and later excluded 20% of them after randomization because of noncompliance, loss to follow-up, and subject withdrawal from the study.

In the current study we have an adequate sample size and include all patients in the final analysis, except six (1.8%) who did not return for follow-up. This makes it unlikely that bias plays a significant role in the decision to withdraw a subject from analysis. It also gives information on the effectiveness of pyridoxine in the treatment of nausea and vomiting of pregnancy under ordinary circumstances when subjects are allowed to accept or reject treatment as they might ordinarily do. In our study we used visual analog scales to quantify the change in the severity of nausea, because the scale can give an objective measure of the severity of nausea and

because it has construct validity and is reproducible.[13-15] We chose a study period of 5 days because the previous study[6] shows that the effect of pyridoxine is evident within a few days of treatment and too long a study period will only result in a higher rate of subject noncompliance and loss to follow-up. Our results showed a significant improvement in mean nausea scores in subjects who received pyridoxine compared with those who received placebo. Pyridoxine also significantly reduced the mean number of vomiting episodes during the first 3 days of treatment, but the beneficial effect appeared to diminish over time. However, with large SDs, as shown in Table III, it is difficult to be certain that the effectiveness does indeed decrease with time. The apparent decrease in the effect of pyridoxine may also be because the severity of the nausea and vomiting of pregnancy fluctuates over time and has a tendency to improve as pregnancy advances.

On the basis of our study, we recommend the use of pyridoxine as a first-line treatment for nausea and vomiting of pregnancy. We suggest that the drug be given on an intermittent basis for a period of 2 to 3 days, followed by a period of rest.

REFERENCES

1. Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC III. Williams' obstetrics. 19th ed. London: Prentice Hall International, 1993:22-3.
2. Fairweather DVI. Nausea and vomiting in pregnancy. Am J Obstet Gynecol 1968;102:135-75.
3. Willis RS, Winn WW, Morris AT, Newsom AA, Massey WE. Clinical observations in treatment of nausea and vomiting in pregnancy with vitamin B_1 and B_6: a preliminary report. Am J Obstet Gynecol 1942;44:265-71.
4. Weinstein BB, Wohl Z, Mitchell GJ, Sustendal GF. Oral administration of pyridoxine hydrochloride in the treatment of nausea and vomiting of pregnancy. Am J Obstet Gynecol 1944;47:389-94.
5. Dorsey CW. The use of pyridoxine and suprarenal cortex combined in the treatment of the nausea and vomiting of pregnancy. Am J Obstet Gynecol 1949;58:1073-8.
6. Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. Obstet Gynecol 1991;78:33-6.
7. Vellacott ID, Cooke EJA, James CE. Nausea and vomiting in early pregnancy. Int J Gynecol Obstet 1988;27:57-62.
8. Jewell MD. Debendox (Bendectin) for nausea in pregnancy. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, eds. Pregnancy and childbirth module. Disk issue 1. Cochrane Database of Systematic Reviews': Review No 03351, 30 April 1993. Oxford: Cochrane Updates on Disk, 1994. (Cochrane database of systematic reviews, review no 03351.)
9. Skolnick A. Key witness against morning sickness drug faces scientific fraud charges. JAMA 1990;263:1468-73.
10. Renault JY, Melcion C, Cordier A. Limb bud cell culture for in vitro teratogen screening: validation of an improved assessment method using 51 compounds. Teratogenesis Carcinog Mutagen 1989;9:83-96.
11. Budroe JD, Shaddock JG, Casciano DA. A study of the potential genotoxicity of methapyrilene and related antihistamines using the hepatocyte/DNA repair assay. Mutat Res 1984;135:131-7.
12. Niebyl JR, Maxwell KD. Treatment of the nausea and vomiting of pregnancy. In: Niebyl JR, ed. Drug use in pregnancy. 2nd ed. Philadelphia: Lea & Febiger, 1988: 11-9.
13. Guyatt GH, Townsend M, Berman LB, Keller JL. A comparison of Likert and visual analogue scales for measuring change in function. J Chron Dis 1987;40:1129-33.
14. Aitkin RCB. A growing edge of measurement of feelings. Proc R Soc Med 1969;62:989-96.
15. Streiner DL, Norman GR. Health measurement scales—a practical guide to their development and use. Oxford: Oxford University Press, 1989:23-5.