FINAL REPORT

VITAMIN B6 FOR NAUSEA AND VOMITING OF PREGNANCY

A RANDOMIZED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL

BY

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Abstract

Objective: To determine the effectiveness of pyridoxine for the treatment of nausea and vomiting of pregnancy

Methods: During an 11-month period, 342 women who first attended antenatal clinic at ≤17 weeks gestation, were randomized to receive either oral pyridoxine hydrochloride 30 mg/d or identical-appearing placebo in a double-blind fashion. Patients graded the severity of their nausea using visual analogue scale and recorded the numbers of vomiting episodes over the previous 24 hours before treatment and again during five consecutive days on treatment.

Results: There was a significant decrease in the mean of post-therapy minus baseline nausea scores in the pyridoxine as compared with that in the placebo group (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.

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

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ABBREVIATIONS

95% CI	=	95% Confidence Interval
mg	=	milligram
ml	=	milliliter
N or n	=	number of cases
SD	=	Standard deviation
VAS	=	Visual Analogue Scale

CHAPTER 1
INTRODUCTION

Background:

Nausea and vomiting is a common and annoying symptom often observed in the first half of pregnancy (1). Because it is so common, nausea and vomiting during pregnancy has been accepted as a presumptive evidence of pregnancy (2). Typically it commences between the first and second missed period and continues until about the fourth missed period (1). The incidence, reported by various authors (3-7), ranges from 45% to as high as 89.4%. Although not a life-threatening condition, nausea and vomiting of pregnancy remains a cause of much discomfort and concern to the pregnant woman and her family. In one report, a quarter of those with symptoms required time off work, suggesting that considerable disruption of work may occur in many women during the early part of pregnancy (7).

Despite considerable researches over the last two decades to determine the etiological factors involved in nausea and vomiting of pregnancy, the results have been inconclusive (7). Hormonal changes of pregnancy have been postulated to play a role. Chorionic gonadotropin (hCG), for instance, has been implicated on the basis that its levels are rather high at the same time that nausea and vomiting are most common (1). Indeed, Mason et al (8) found statistically higher hCG levels in women with nausea and/or vomiting than in asymptomatic women. However, Soules et al (9) and Depue et al (10) found no relationship between the serum levels of hCG and the incidence and severity of nausea and vomiting in pregnant women. The few studies on estradiol and progesterone are also contradictory (8, 10, 11). Overall the relationship of this condition to the presence of increased concentrations of circulating hormones is not clear (2). Since nausea and vomiting often present before a woman realizes that she is pregnant, it is unlikely that psychogenic factors play a primary role (12). However, emotional factors undoubtedly can contribute to the severity of the symptom. It has been noted that as many as 80% of patients with severe hyperemesis during pregnancy have identifiable contributing psychologic disturbances (2).

As might be expected in a condition of unknown etiology, a multitude of treatments have been empirically recommended, reflecting the various theories as to the underlying cause. Fairweather (13) lists studies (many of them uncontrolled) on 30 different treatments, including various hormones, vitamins, amphetamines, phenothiazines and antihistamines etc. Given that pregnancy nausea and vomiting

is a self-limited condition, it is not surprising that uncontrolled trials have yielded rather spectacular results. For example, Finch (14) found that 91% of patients were relieved by desensitization with corpus luteum extracts. Hawkinson (15) reported essentially the same benefit with estrogens and Shute (16) achieved an 80% rate of cure with testosterone.

In contrast to the results obtained in the uncontrolled trials, those from controlled trials have not been quite impressive. King (17) compared methamphetamine, meclozine and placebo. He found no evidence of a beneficial effect in the active preparations. His "improvement or cure" was 23/32 (68%) with methamphetamine, 53/60 (88%) with meclozine and 48/58 (83%) in the two placebo groups combined. In a double-blind trial of meclozine and pyridoxine compared with pyridoxine alone, the General Practitioner Research Group (18) found these two treatments to have virtually identical effects: 27/40 (68%) of women obtained relief with the pyridoxine-antihistamine combination and 25/36 (69%) with pyridoxine alone.

By far the most widely used drug to treat nausea in pregnancy was, until recently, Debendox (marketed as Bendectin in the United States by Merrell Dow Pharmaceuticals, Inc, Cincinnati, Ohio) (19,20). Indeed, Debendox was the most widely used prescription drug of any kind taken in pregnancy (20). At its peak use, an estimated 20-25% of pregnant women in the United States used Bendectin. Bendectin was the only drug approved by the US Food and Drug Administration for the treatment of nausea during pregnancy (21). First sold in 1956, the drug originally contained the antispasmodic agent dicyclomine hydrochloride, the antihistamine doxylamine, and pyridoxine hydrochloride (vitamin B6). Dicyclomine was dropped from the US formulation in 1977 because placebo-controlled trials showed that component by itself has no significant therapeutic effect (21). The two-component Debendox was removed from the market in June 1983 as a direct result of the onslaught of hundreds of lawsuits brought against the manufacturers, claiming that the drug had caused congenital malformations in the offspring of women who had used it (19,21). So far, nineteen epidemiological studies of Debendox and congenital malformations in offspring have been done with the conclusion that Debendox is not associated with an increased risk of congenital malformation (19). However, it should be remembered that epidemiologic studies are able to identify only strong teratogens; the identification of weak ones requires unrealistically large sample sizes. So the question whether Debendox is absolutely safe in pregnancy remains unanswered (21).

Rationale for the proposed study:

According to the Cochrane Database of perinatal trial, there have been only 3 controlled trials of Debendox. The overview of these three trials provides strong evidence that Debendox gives considerable relief for nausea and vomiting in pregnancy (typical odds ratio = 0.3, 95% confidence interval 0.16-0.54) (19). The remaining question is which of the two components in Debendox, the antihistamine doxylamine or pyridoxine (Vitamin B6), or both is (are) the active ingredient(s). This is more than just academic curiosity because some recent studies (22,23) raise the concern that doxylamine (the antihistamine in Debendox) may be teratogenic. On the contrary, the available evidence does not support a teratogenic risk from ingestion of vitamin B6 during pregnancy (24).

Pyridoxine (vitamin B6) is a water-soluble B complex vitamin that is an essential coenzyme in the metabolism of aminoacids, carbohydrates and lipids (25). The first use of pyridoxine for severe nausea and vomiting of pregnancy was reported by Willis et al (26) in 1942. In an uncontrolled study, they used parenteral vitamin B1 and B6 to treat nausea with almost complete relief. Several other similarly uncontrolled studies (27-31) in the same decade also suggested efficacy from the use of vitamin B6. In 1963 the General Practitioner Research Group (18) reported a double-blind trial of meclozine (an antihistamine) and pyridoxine compared with pyridoxine alone. They found these two treatments to have virtually identical effects and correctly concluded that " it would be of interest to compare pyridoxine with placebo". We have been able to identify only one randomized, double-blind placebo-controlled trial of vitamin B6 for the treatment of nausea and vomiting of pregnancy in the English literature. In this report, Sahakian et al (25) found that there was a significant reduction in nausea scores between patients with severe nausea receiving vitamin B6 and placebo ($p < 0.01$). However they did not find a significant difference between treatment and placebo in patients with mild to moderate nausea and in the group as a whole. We feel that the result of this study is still inconclusive because of the following reasons:

1. The study recruits 74 subjects and later excludes 15 of them (20.3%) after randomization because of non-compliance and lost to follow-up. Since the reasons for withdrawal in each group may be different, the subjects remaining in the trial may not be comparable. Moreover, omitting these subjects from analyses, as was done in this case, can seriously bias the result of the study.
2. The study includes too few subjects and has a statistical power of only about 30% to detect any treatment effect if it indeed exists.

3. In this study there is no significant treatment effect when analysis was performed on all 59 women who completed the protocol. Nevertheless, the investigators went on to do subgroup analyses by classifying patients with nausea scores ≥7 as severe and those with nausea scores <7 as mild to moderate nausea subgroup. Because cutoff scores can be arbitrarily set at any level, it is theoretically possible to do many such comparisons and therefore tests of significance become difficult to interpret. Such post hoc analysis should serve primarily to generate hypothesis for further evaluation in future studies and must be interpreted cautiously. We, therefore, cannot concur with the authors' conclusion that pyridoxine is effective in the treatment of nausea in patients in the severe nausea subgroup.

In conclusion there is a surprisingly small number of controlled trials for such prevalent and discomforting symptoms like nausea and vomiting of pregnancy. New trials are urgently needed to identify efficacious and safe therapy. There is some evidence from case series that vitamin B6 may be effective in this regard. Unfortunately, the only randomized trial for B6 is too small and does not have enough statistical power to show treatment effect. It is, therefore, appropriate to propose a randomized placebo-controlled trial of vitamin B6 for nausea of pregnancy.

Specific Objective of the research project

To determine the effectiveness of vitamin B6 for the treatment of nausea and vomiting of pregnancy.

CHAPTER 2
METHODOLOGY

Research Design:

Design architecture and methodology

Design architecture : A randomized double-blind placebo-controlled trial

Study population: Pregnant women with nausea and vomiting of pregnancy, who attended the antenatal clinic at Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University between May 24th, 1993 and April 1st, 1994.

Eligibility criteria: All pregnant women with nausea and vomiting of pregnancy were included in the study if they fulfilled the following inclusion and exclusion criteria:

Inclusion criteria: The study included pregnant women who

1. had gestational age ≤ 17 weeks of pregnancy;
2. stated that they would be able to attend follow-up visit as planned.

Exclusion criteria: The study excluded pregnant women who

1. had other medical conditions such as hepatitis or gastrointestinal diseases that might manifest itself 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 not be able to take the medication as prescribed;
5. refused to enter the trial.

Experimental manoeuvre: Patients were recruited from the antenatal clinic by care-providing physicians and nurses. All consecutive patients meeting eligibility requirement were asked to participate in the study. After obtaining informed consent, patients underwent a general physical examination and routine obstetric evaluation.

Patients were then randomized into 2 groups using a table of random numbers. Patients in the vitamin B6 group received twenty 10-mg tablets of pyridoxine hydrochloride, to be taken orally one tablet every 8 hours starting the following morning. They were given instructions to take the medication between 6-8 am, 2-4 pm and 10-12 pm for 5 days. Patients in the placebo group received identical appearing tablets in the same regimen. The patients in both groups were advised to divide their meals into frequent small ones rich in carbohydrates and low in fat.

Patients were asked to grade the severity of their symptoms in the visual analogue scale as shown in Appendix 1. They rated their nausea by marking "X" on the vertical line (10 cm in length), anchored with 0 = no nausea and 10 = nausea as bad as it could be, corresponding to their perceived state. The first documentation was recorded on the initial visit to reflect the severity of nausea over the last 24 hours. On the following five days, recording of the severity of nausea were done twice daily i.e. at noon and at bedtime. Along with grading nausea, all patients were requested to record the number of episodes of emesis for the 24 hours prior to their initial visit and also on each subsequent days. Patients were asked to return in one week to assess their response to treatment. Those who defaulted were contacted by telephone call or by mail.

Blinding and codebreaking: In this study, neither the patients nor the physician knew the identity of the intervention. Both vitamin B6 and the placebo, a look-alike of vitamin B6, were prepared by the hospital pharmacy and were packed similarly in an envelope containing 20 tablets each. Before the trial began, a code for each patient was prepared and kept in a sealed black envelope that could not be read through. The two medications were coded as drug A and drug B. The patients received medications from a research assistant without the physician seeing the tablets. A list that revealed drug codes given to the patients was kept by the assistant and was not accessible to the physicians.

Avoidance of cointervention and contamination: Contamination was minimized by asking patients not to take any other medications outside the trial and by double-checking to ensure that study drugs were correctly dispensed. Since this was a double-blind trial, significant problem of cointervention was unlikely.

Compliance: In this study, compliance in taking the medication was not a big problem because patients were requested to take one small tablet (which was odorless and tasteless) three times a day for a relatively short period of time (only 5 days). To further enhance compliance, sufficient time was given to subjects to clearly inform them about the importance of their taking the medication as prescribed. Compliance was assessed by pill count and by monitoring attendance at scheduled visits.

Outcome measurement: The primary outcome in this study was the change in the severity of nausea which was subjective in nature. One major issue in measuring this variable was to select the optimal response options. Possible choices include:

1. A binary response such as improve or not improve.
2. Verbal description of how the patient feels.

3. Multi-item Likert scales such as no improvement, slight improvement, moderate improvement and marked improvement etc.
4. Visual analogue scales (line anchored at either end by the extremes of the dimension being measured - no nausea, worst possible nausea - along which the subjects are asked to place a mark to indicate their status).

Only options 3 and 4 are good candidates because we need an instrument that has the ability to detect clinically important change even if that change is small. In this study, Visual analogue scales (VAS) was chosen as the measuring tool because it has the following advantages (32-34):

1. This method has been shown to be very reproducible (i.e. the test consistently yields more or less the same results when administered on several occasions to stable subjects;
2. The method has been shown to have construct validity (i.e. it relates to other tests or measures such as the Likert scales in the way one would expect if it is really measuring what it is supposed to measure);
3. The markings on each of the visual analogue scales can be measured in centimeters, thus obtaining an objective measure of the severity of nausea.

Secondary outcome in this study was the number of episodes of vomiting which could be objectively counted by the patients themselves. Since this was a double-blind trial, bias in the measurement of outcome was unlikely.

Sample size calculation: In the trial by Sahakian et al (25), the mean differences in nausea scores using VAS scales (baseline - post-therapy) for the vitamin B6 (31 subjects) and the placebo group (28 subjects) were 2.9 ± 2.4 and 1.9 ± 2.0 respectively (mean ± SEM). To show this treatment effect with a probability of type I error of 5% ($Z_{\alpha} = 1.96$, two tailed) and a probability of type II error of 20% (i.e. a power of 80%, $Z_{\beta} = 0.84$), the following number of subjects per group (N) is needed:

$$N = \frac{2(Z_{\alpha} + Z_{\beta})^2 \sigma_d^2}{(\mu_{dc} - \mu_{dt})^2}$$

where μ_{dc} = the true value of the difference in the nausea scores at baseline and after treatment for the control (placebo) group, which will be estimated to be 1.9.

μ_{dt} = the corresponding value for the vitamin B6 group, estimated to be 2.9.

π_d^2 = variance of the difference in the nausea scores at baseline and after treatment for the control and the vitamin B6 group, which is not known but can be estimated from the data in the trial by Sahakian et al (25), using the formula:

$$\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}$$

where s_1 is the standard deviation of the difference in nausea scores in the control group and n_1 the number of subjects in the control and s_2 and n_2 are corresponding values for the vitamin B6 group

$$N = \frac{2(1.96 + 0.84)^2 \times 9.76}{(1.9\text{-}2.9)^2}$$

$$N = 153$$

Allowing for a 10% drop-out rate, the total number of patients required in this study is [1/(1-0.1)] x 2 x 153 = 340.

Data handling and analysis: Patients' data were entered on standardized forms (Appendix 2) and checked for completeness by the clinician and subsequently forwarded to the research assistant who entered data into dBase IV program on an IBM PC on a weekly basis. All data were backed up on floppy disk once a month and kept in a secure place. Data analysis was done using BMDP program on an IBM PC. Student t-test was used to compare mean difference in post-therapy minus baseline nausea scores in the two groups and the result was considered significant at a value of $P < 0.05$. The number of subjects who had vomiting in the two groups were compared using Chi square test. Analysis of the result was done on the basis of intention to treat, ie all patients remained in their respective groups after randomization and were included in the analysis.

Ethics:

The subjects were informed orally of the purpose and the procedures of the study before they consented to participate (Appendix III). They were assured of the confidentiality of any information obtained and of their right to withdraw from the study without penalty. The study was approved by the ethical committees of the Faculty of Medicine, Chiang Mai University.

CHAPTER 3
Results

Out of 3321 pregnant women who first attended antenatal clinic at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University between May 24th, 1993 and April 1st, 1994, only 342 cases met the eligibility criteria and consented to participate in the study. Of these, 169 patients were assigned to the placebo group 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 1)

Table 1 : Baseline characteristics of the patients

	Placebo (n = 167)	Pyridoxine (n = 169)
Age (y)	27.1 ± 5.4	26.9 ± 5.2
Parity		
Primipara	84 (50.3%)	80 (47.3%)
Multipara	83 (49.7%)	89 (52.7%)
Gestational age (weeks)	10.97 ± 2.8	10.98 ± 2.7
Duration of nausea (weeks)	3.9 ± 2.7	3.8 ± 2.4
Baseline nausea scores	4.9 ± 2.4	5.2 ± 5.3
No. of vomiting in the previous 24 hours	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 N (%)

On follow-up visits, one patient in each group did not rate her nausea scores on treatment day 3, while two in the placebo and one in the pyridoxine group did not record their scores on both days 4 and 5 of treatment. Mean differences in nausea scores obtained by subtracting post-therapy nausea scores from baseline scores in the pyridoxine group were significantly higher than those in the placebo group. (Table 2)

Table 2: Mean difference in nausea scores in the placebo and pyridoxine groups

		n	Mean difference in nausea score (baseline - post-therapy)	P
Day 1	Placebo group	167	1.2 ± 2.4	0.0001
	Pyridoxine group	169	2.2 ± 2.1	
Day 2	Placebo group	167	1.7 ± 2.8	0.0002
	Pyridoxine group	169	2.8 ± 2.3	
Day 3	Placebo group	166	2.1 ± 3.0	0.0011
	Pyridoxine group	168	3.0 ± 2.4	
Day 4	Placebo group	165	2.5 ± 3.2	0.0282
	Pyridoxine group	168	3.2 ± 2.6	
Day 5	Placebo group	165	2.7 ± 2.9	0.0421
	Pyridoxine group	168	3.3 ± 2.7	
Average	Placebo group	167	2.0 ± 2.7	0.0008
Day 1-5	Pyridoxine group	169	2.9 ± 2.2	

One hundred and eleven women out of 169 in the vitamin B6 group and 108 out of 167 in the placebo group had one or more vomiting episodes during the past 24 hour prior to treatment (Pearson Chisquare = 0.038, p = 0.8640). After 5 days of treatment, the proportions of women who experienced vomiting in the two groups (61/168 in the vitamin B6 versus 56/165 in the placebo group respectively; three cases had missing data) were not statistically different (Pearson Chisquare = 0.205, p = 0.6506). However, when we substract the numbers of post-therapy vomiting episodes from baseline values and calculate the mean reduction, there was a statistically significant reduction in the vitamin B6 than that in the placebo group during the first three days of treatment, but not on the fourth and fifth days. Again the overall mean reduction in the number of vomiting episodes over the 5-day treatment period did not reach statistical significance (Table 3)

Table 3: Mean reduction in the number of vomiting episodes in the placebo and the vitamin B6 (pyridoxine) groups

		n	Mean reduction in vomiting episodes (baseline - post-therapy)	P
Day 1	Placebo group	111	0.07 ± 2.5	0.0469
	Pyridoxine group	112	0.67 ± 1.9	
Day 2	Placebo group	111	0.32 ± 3.0	0.0142
	Pyridoxine group	112	1.17 ± 2.1	
Day 3	Placebo group	110	0.64 ± 2.9	0.0237
	Pyridoxine group	111	1.42 ± 2.1	
Day 4	Placebo group	109	1.15 ± 2.3	0.1537
	Pyridoxine group	111	1.59 ± 2.2	
Day 5	Placebo group	109	1.34 ± 2.3	0.7594
	Pyridoxine group	111	1.44 ± 2.6	
Average	Placebo group	111	0.65 ± 2.4	0.0552
Day 1-5	Pyridoxine group	112	1.22 ± 2.0	

There was 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 out of 167 or 54.5% in the placebo versus 102 out of 169 or 60.4% in the pyridoxine group). Compliance in this study was assessed by pill count and by monitoring attendance at scheduled visits. Pill count revealed that 139 out of 167 patients (83.2%) in the placebo group took at least 15 out of the 20 prescribed tablets as compared to 141 out of 169 (83.4%) in 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. Of those who returned, four in the placebo and five in the pyridoxine group were late for their scheduled appointments.

CHAPTER 4
Discussion

Nausea and vomiting in pregnancy is a common and annoying symptom. It usually begins early in pregnancy and continues until about the fourth month (1). Despite considerable researches, the etiology of this symptom remains unknown, and it is possible that more than one mechanism may be involved (7). Given that pregnancy nausea and vomiting is a self-limiting condition, it is not surprising that uncontrolled trials of various treatments have yielded rather impressive results (19).

Many uncontrolled studies (26-31), suggest that pyridoxine may be effective in the treatment of nausea and vomiting of pregnancy. Pyridoxine was included in the formulation of Debendox (previously marketed as Bendectin in the United States by Merrell Dow Pharmaceuticals), which was the only drug approved by the US Food and Drug Administration for the treatment of nausea during pregnancy (19-21). 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 US formulation because plcebo-controlled trials showed that the component by itself had no significant therapeutic effect (21). According to the Cochrane Database of perinatal trial, there have been only 3 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 = 0.16-0.54). The remaining question is which of the two components in Debendox, the antihistamine doxylamine or pyridoxine (Vitamin B6), or both, is (are) the active ingredient (s). This is more than just academic curiosity because some recent studies (22, 23) raise the concern that doxylamine may be teratogenic. On the contrary, the available evidence does not suggest a teratogenic risk from the ingestion of vitamin B6 during pregnancy (24).

To our knowledge, there has been only one randomized, double-blind placebo-controlled trial of vitamin B6 for the treatment of nausea and vomiting in pregnancy in the English literature. In that study, Sahakian et al (25) reported a significant reduction in mean nausea scores in subgroup of patients with severe nausea who received vitamin B6 as compared with placebo ($p<0.01$). 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. Moreover, the study included only 74 subjects and later excluded 20% of them after

randomization because of noncompliance, lost to follow-up, and subject withdrawal from the study. To show their treatment effect with a probability of type I error of 5% (two-tailed) and a probability of type II error of 20% (ie a power of 80%), they need to recruit at least 300 patients.

In the current study we have adequate sample size and include all patients in the final analysis, except six (1.8%) who did not return for follow-up. This eliminates the question whether bias plays a role in the decision to withdraw a subject from analysis. It also gives information on the effectiveness of vitamin B6 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 employ visual analogue scales (VAS) 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 (32-4). We chose a study period of 5 days because the previous study (25) shows that the effect of vitamin B6 is evident within a few days of treatment and longer study period will only result in higher rates of subject noncompliance and loss to follow-up. Our result showed a significant improvement in mean nausea scores in subjects who received vitamin B6 as compared with those who received placebo. Vitamin B6 significantly reduced the mean numbers of vomiting episodes during the first three days of treatment but the beneficial effect appeared to diminish over time and was not statistically significant on day 4 and 5 of the study. This may be due to the fact that pregnancy nausea and vomiting is a self-limited condition and has a tendency to improve as pregnancy advances. Based on our result, we recommend the use of vitamin B6 as a first-line treatment for nausea of pregnancy.

CHAPTER 5
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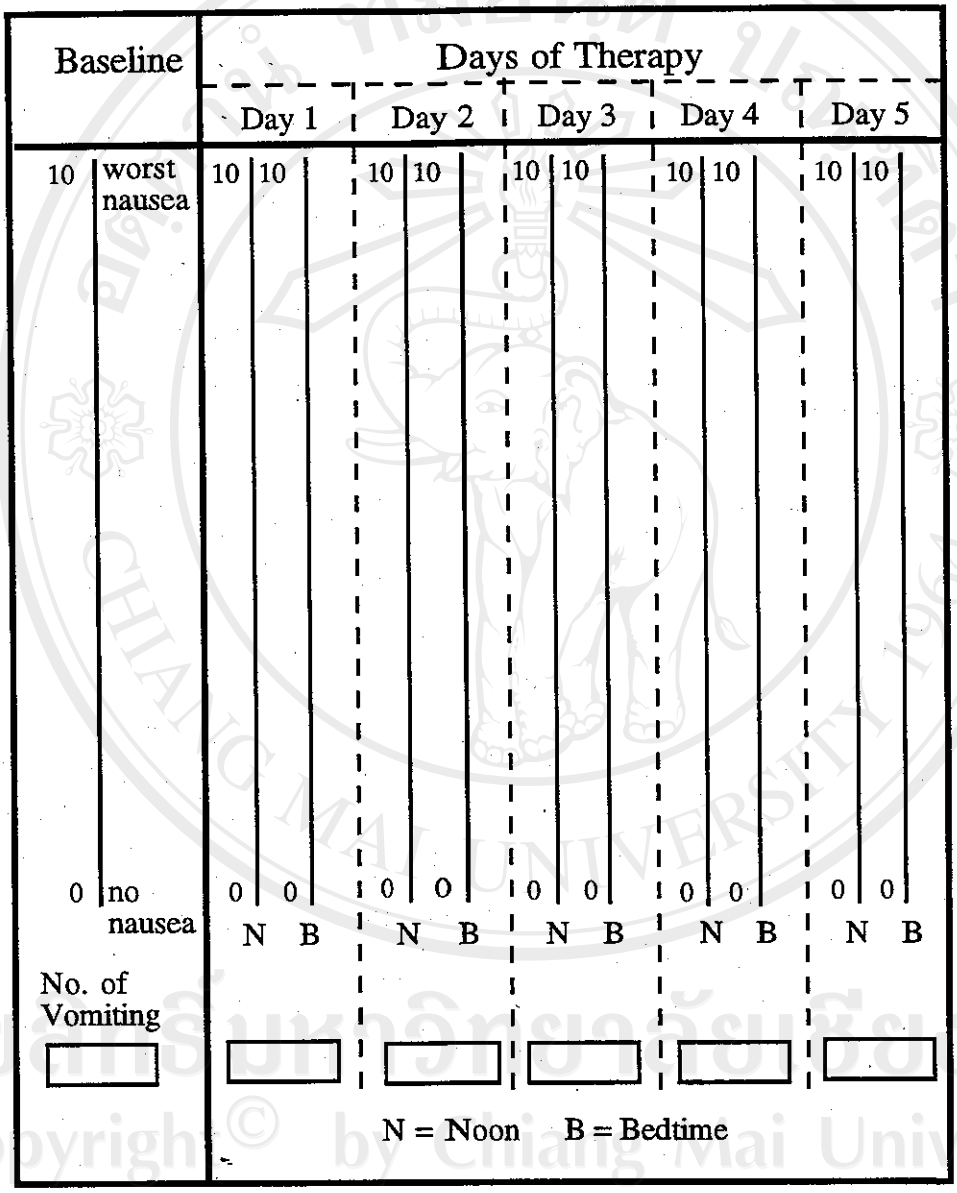
CHAPTER 6

Appendix I

Visual Analogue Scale for Grading Nausea



Appendix II

Data Form for Vitamin B6 Trial

Date of entry (d d - m m - y y) ☐☐ - ☐☐ - ☐☐ Code No ☐☐☐

Name ..... ☐☐☐☐

Age ☐☐ years HN ☐☐☐☐☐☐☐

Parity (1=primipara, 2=multipara) ☐

Gestational Age in weeks ☐☐ Duration of nausea/vomiting ☐☐ wks

Place of residence ..... ☐☐☐

Educational level ..... ☐☐

Occupation ..... ☐☐

Baseline Nausea score ☐☐ • ☐ cm. No. of vomiting at baseline ☐☐☐

Date of follow-up (d d - m m - y y) ☐☐ - ☐☐ - ☐☐

	No. of vomiting	Nausea Scores (N)	Nausea Scores (B)	Average Scores
Day 1:	☐☐☐	☐☐ • ☐ cm	☐☐ • ☐ cm	☐☐ • ☐ cm
Day 2:	☐☐☐	☐☐ • ☐ cm	☐☐ • ☐ cm	☐☐ • ☐ cm
Day 3:	☐☐☐	☐☐ • ☐ cm	☐☐ • ☐ cm	☐☐ • ☐ cm
Day 4:	☐☐☐	☐☐ • ☐ cm	☐☐ • ☐ cm	☐☐ • ☐ cm
Day 5:	☐☐☐	☐☐ • ☐ cm	☐☐ • ☐ cm	☐☐ • ☐ cm

Patient Compliance:

Take all medication as prescribed (1=No, 2=Yes) ☐

If no, how many tablets were taken ☐☐

Visit Clinic on Appointment (1=No, 2=Yes) ☐

Divide food intake into multiple small meals as recommended

☐ Yes ☐ No

Notes: .....

.....

Appendix III
Consent for Vitamin B6 Trial

Before giving their consents, the subjects will be explained orally as follows:

" You have been asked to participate in a study to assess the effectiveness of vitamin B6 in the treatment of nausea and vomiting in pregnancy. Vitamin B6 has been used to treat this condition for more than 50 years but without solid evidence that it really works. As far as we know, vitamin B6 is quite safe in pregnancy at the dose given in this trial and is currently in use both in our institution and abroad.

If you agree to participate, you will be randomly allocated to a group that receives vitamin B6 or placebo (no active drug). Subjects in both groups will receive standard antenatal care and will be appointed to come back for one follow-up visit within one to two weeks after entry into the trial. With your permission, an optional specimen of blood (5 ml) will be obtained at study entry and again at the first follow-up visit. There will be no tissue sampling in this study. The drug or placebo will be given to you at no cost, to be taken three times per day for five days. You will be asked to record the severity of nausea four times daily and the number of vomiting once a day for five days during the trial.

All information regarding your case will be treated confidentially. You may refuse to participate or withdraw from this study at any time without prejudice to your future care at this hospital"

After that the patient, if she agrees to participate in the study, will sign a consent form in front of a witness.