Vitamin B_6 for Side Effects of Oral Contraceptives

Abstract

Family planning helps to improve the health of children and women. In Cambodia the most popular method is the oral pill, but many women don't use it because they are afraid of side effects like headache, nausea, dizziness, no appetite, hot feelings, and vomiting. An experiment was done in Phnom Penh with 47 new pill users who were randomly assigned to control and intervention groups. The control group was given a placebo, and the intervention group took vitamin B_6 25 mg once a day. All clients were followed up after a month to see if they had any side effects. The result shows a large difference between the control and intervention groups. The intervention group had much less side effects than the control group and the results showed statistical significance for nausea, dizziness, hot feelings and no appetite. Headache was also less in the intervention group but not statistically significant. Phnom Penh clinics should give Vitamin B_6 to clients who use the conceptive pill, because it will reduce side effects and more women will use family planning, which will help the health of children and women in Cambodia. The same kind of study should be done in the rural areas of Cambodia to see if the results are the same there as in Phnom Penh. A similar study should also be done for other hormonal contraceptives like Depo-Provera injection and Norplant.

I. Background

Family planning allows women to plan how many children they want and when they want to have them. It is important for the health of mothers and children. If women can have only the children they want, they can feed their children more and the children will be healthier and happier.

If women don't want to have a baby and they become pregnant, they may have an abortion. This causes many women to die because some women are poor or shy, so they don't go to a real hospital. Instead they go to a person who doesn't know clearly how to do it or uses instruments that are not clean at all. If a woman doesn't want to have children but has them anyway, it might make her unhappy and she may not take care of the children carefully. Family planning also allows a woman to have enough time between pregnancies. This is very important for both mother and children, because if women have children with not enough time between pregnancies, they don't have enough vitamins, iron and strength. They might be unhealthy during pregnancy and be unable to take care of their children properly.

For children, both the child already born and the new child are in danger if pregnancies are too close together. The first child might get not enough milk to drink from the mother, because the mother has to feed another child. It may make the first child unhealthy from not enough food and care. The second child might be born too small, with less than normal birth weight and more vulnerable to infection. Research shows death rates for babies that were born less than 2 years after another are 54 percent higher than for babies born more than two years apart.

II. Introduction

According to the Cambodia Demographic and Health Survey (CDHS) done by the Ministry of Health (MOH) in 2000, 48.6% of married woman in Cambodia don't want to become pregnant now, 35.2% don't want to become pregnant again ever, and 13.4% want to but

later. However, only 23.8% of married women use a method of family planning and only 18.5% use a modern method. The main reason why Cambodian women who don't want to become pregnant don't use family planning is that they are afraid of side effects. Over thirty-two percent of Cambodian women gave that reason in the CDHS 2000. It was the same in the National Survey Health 1998. Another survey in 1995 done by the Ministry of Health asked women who used to use family planning and stopped why, and the main reason was side effects (39.3%).

In Cambodia the methods of family planning that are available are: condom, intra-uterine device (IUD), sterilization, injection, and oral pill. Condoms, IUD, and sterilization, however, are difficult for Cambodian women to use. For IUD, the woman has to go to a clinic, spend a lot of money and a lot of time. For sterilization, the woman has to have an operation at a hospital and it is permanent, she can't have children later. Condom use is not a popular method in Cambodia and it depends on the man. So the most popular methods for Cambodian women are injection and oral pill. Injections need a health worker, but oral pills can be bought from the market cheaply and are easy to take.

Pregnancy can happen when an egg comes out from the ovaries and is fertilized by a man's sperm. Oral contraceptives prevent ovulation (release of the egg from the ovary). Ovulation is controlled by the anterior pituitary gland which releases Follicle Stimulating Hormone (FSH) according to the amount of the hormone estrogen in the body (feedback mechanism). When estrogen is low, FSH is released and causes ovulation. The contraceptive pill contains estrogen so the pituitary glad doesn't release FSH, so no ovulation, no fertilization and no pregnancy. The contraceptive pill has a few serious effects such as high blood pressure or stroke, but it is very rare and doctors can identify women who are likely to have such serious problems. However, many women may have small side effects like: headache, vomiting, nausea, feeling hot in their bodies, and no appetite.

Nausea and vomiting can happen because high estrogen in the blood can set off the chemoreceptor trigger zone (CTZ) in the brain which sends a signal through neurotransmitters (chemicals in the brain) to the vomiting center in another part of the brain, the medulla oblongata. Headaches may happen because when the levels of estrogen change quickly, it causes changes in neurotransmitters that are involved in pain signal such as serotonin and gamma-aminobutyric acid (GABA). When women take the oral contraceptive pill (OC), they take it for 21 days which makes estrogen levels high, but then they stop for 7 days and the estrogen level drops quickly.

Since Vitamin B_6 is necessary for synthesis of these same neurotransmitters, Vitamin B_6 deficiency might also be a factor in causing side effects of OCs. More than 100 studies have shown that the contraceptive pill decreases vitamin B_6 in the body and interferes with vitamin B_6 metabolism. In a study in Sudan (a very poor country in Africa), 70% of women that used OCs were vitamin B_6 deficient and the ones that had the deficiency had more side effects. Cambodians like to eat mostly white rice, so many women in Cambodia probably also lack B vitamins even before they start to take OCs.

Vitamins are coenzymes. They bind to receptor sites on different enzymes in the body. Estrogen competes with vitamin B_6 to bind with the enzyme receptors. The more estrogen, and the less Vitamin B_6, that there is in the body, then the more chance for estrogen to bind with the receptor first and block the action of the Vitamin B_6. Vitamin B_6 is necessary for nearly 100 enzymatic reactions. It is important for release of energy from food, red blood cell formation, and also it helps make many neurotransmitters (chemicals that control the brain).

In a controlled study in England, it was proven that vitamin B_6 reduces depression (sad feeling) in women taking OCs. Many studies have shown that giving vitamin B_6 helps nausea from pregnancy. Several studies have found that giving 25-30 mg once a day of vitamin B_6 can also reduce other side effects in women that use OCs, but most of those studies did not have a control group A control group is important because these side effects are subjective. Some people might feel better just because they expect to when they have medicine. So it is important to have two groups for comparison: one that is given the vitamin and another that is given a placebo (something that looks like medicine but has nothing in it).

Only one controlled study has been done in Mexico in 1997. The results found that the Vitamin B_6 group had fewer side effects than the placebo group but the difference was not statistically significant. This means that it is not possible to say that the difference seen in the sample is really the same for the whole population. The sample was small (62 Vitamin B6 and 62 placebo) and the amount of difference found for that size sample is not enough to be sure. Also, the women in the study had average weight of 56.9 kg compared to Cambodian women taking the pill which are only an average of 49.5 kg (2000 CDHS), and the food they eat in Mexico is quite different from in Cambodia so we cannot assume that results there apply to Cambodia. No studies have been done yet in Cambodia. This study will attempt to replicate the study done in Mexico in Cambodia under Cambodian conditions.

III. Hypothesis:

Supplemental vitamin B_6 will help reduce side effects in Cambodian women using birth control pills.

IV. Experimental Design

To test the hypothesis that vitamin B_6 would reduce side effects in women who use contractive pills, the experiment compared two groups of women who were just starting to use oral contraceptives. One group (intervention group) was given vitamin B_6 25 mg - one pill a day, and the other group (control group) was given a placebo - one pill a day. A placebo is something that looks like medicine but doesn't affect anything in the body. It is necessary to use a placebo for the control group because the side effects are subjective. Some women may feel better just because they think that they are getting medicine to stop side effects. The placebo that was used in this study is a candy made from milk powder and sugar that looks like a pill.

The women for this experiment were taken from two clinics in Phnom Penh that provide family planning: Reproductive Health Association of Cambodia (RHAC) and Cambodian Women's Clinic (CWC). The clinics' staff explained all the family planning methods and the women made their own choice of which one to use. The women were examined by the clinics' health workers first to make sure that they were able to use the contractive pill safely.

It was planned to have 50 control and 50 intervention clients but only 24 and 23 could be found, because finding clients who were new users was really difficult and took a lot of time. Some days there were one or two clients, and sometimes not even one, because most women who use the pill just buy it at the market and don't come to a clinic.

The women were told about the experiment and how it works. It was up to them whether to be in the study or not. If they agreed, they first signed a consent form. Women who agreed to be in the study were interviewed after about a month to find out if they were feeling any side effects, and ask whether they had been taking the pill and supplement (vitamin or placebo) every day or not. Most interviews were done by telephone but some women didn't have a telephone so they were interviewed in person.

The names of all the women in the study were kept confidential for their privacy.

- The independent variable was taking vitamin B6 or placebo
- The dependent variable was the side effects that the women reported
- The control variables were:
  - how long they have been taking the contraceptive pill
  - whether they took the pill and vitamin/placebo regularly
  - age
  - general health
  - nutrition
  - socioeconomic status
  - counseling about the pill

The control variables were controlled by:

1) The women were in the study only if they were a new user and interviews were done after the same amount of time (about one month).

2) During the follow-up interview the women were asked if they took the pill and vitamin/placebo regularly. All of the women in both the control and intervention group said they had. It is assumed that their answers are true because there is no way to check. If some women didn't answer honestly, it should be the same for both control and intervention groups because they were chosen randomly and they didn't know which group they were in.

3) The clinic checked all the women's health before they let them take the pill and explained how to take it, so the control and intervention groups should be similar for counseling and general health. The clinic staff didn't know which group the women would be in.

4) Nutrition and age couldn't be directly controlled, but the women were from the same clinics and were chosen for intervention or control group randomly, so the two groups were expected to be similar. Age and weight and height were recorded for all women and the body mass index (weight in kilograms divided by height in cm squared) was used to measure nutrition.

5) For socioeconomic status and education it was impossible to control it exactly, but because the control and intervention groups were chosen randomly from women in Phnom Penh going to the same clinics, they should be similar.

V. Results

The data were analyzed by using the SPSS program. First, a data file was made by putting all the variables into the file and then typing in the answers from the follow-up forms. Two new variables were created out of the existing variables:

1) Body Mass Index was calculated using the formula weight divided by the height squared.
2) A total score for side effects was made by giving 0 for no and 1 for yes for each side effect and then adding it.

The data was analyzed in SPSS by making a cross-tabulation for the characteristics of the clients and each of the side effects by control and intervention group. Also a cross-tabulation of the side effect score by control and intervention group was made. The SPSS program automatically calculated a Chi Square value to show if the results were statistically significant or not. The SPSS program calculates a value based on the Chi Square for significance. This value is the percent possibility that the difference could be by accident or if it is probably really true.

Characteristics of Control and Intervention Group Clients

In general it can be said that the two groups was quite similar, as shown below:

Table 1: Comparison of Control and Intervention Group Characteristics

	Mean Age	Mean Height	Mean Weight	Mean BMI
Control Group (N= 23)	28.88	1.55	51.50	21.36
Intervention Group (N= 24)	29.78	1.57	49.61	20.06

Time Between Starting in the Study and Interview

The plan was to interview the women one month after they started in the study and most of them were interviewed after about a month. In 3 cases, however, it was hard to contact the women and so the interview was done late. The mean number of days between starting in the study and being interviewed was 34.9 and the range was 24 – 40 days except for those 3 cases who were finally interviewed 59, 63 and 82 days after starting in the study as shown below:

Table 2: Time Between Start And Follow-Up

Number of Days	Frequency	Percent	Cumulative Percent
24	1	2.1	2.1
28	2	4.3	6.4
29	3	6.4	12.8
30	3	6.4	19.1
31	6	12.8	31.9
32	8	17.0	48.9
33	7	14.9	63.8
34	5	10.6	74.5
35	1	2.1	76.6
36	2	4.3	80.9
37	1	2.1	83.0
38	3	6.4	89.4
39	1	2.1	91.5
40	1	2.1	93.6
59	1	2.1	95.7
63	1	2.1	97.9
82	1	2.1	100.0
Total	47	100.0	
Mean	**34.91**		

Side Effects Reported

The follow-up interview asked specifically whether or not the client had headache, dizziness, hot feelings, nausea, vomiting, or no appetite. It also asked if there were any other side effects besides these. There were only five (5) cases of vomiting in both groups combined, and "other" side effects also had five (5) or less cases, so these were not analyzed further. Headache, dizziness, hot feelings, nausea, and/or no appetite were all reported by more than ten (10) clients so these were analyzed by a comparison between the control and the intervention group. Table 3 shows the percentage in each group with any health complaint:

Table 3: Any health problem by Control and Intervention Group

Any health problem	**Control group** (N = 24)	**Intervention group** (N=23)	**Total**
No	25.0%	56.5%	40.4%
Yes	75.0%	43.5%	59.6%
Total	100.0%	100.0%	100.0%

Pearson Chi-Square Value = 4.846 Significance= p <0.028

As can be seen, there were many more complaints of side effects in the control group and this difference is statistically significant at probability (p) of 0.028. That means that there is only a 2.8% chance that the difference was due to chance.

Table 4 shows the percentage in each group with dizziness:

Table 4: DIZZINESS by Control and Intervention Group

DIZZINESS	**Control group**	**Intervention group**	**Total**
No	45.8%	87.0%	66.0%
Yes	54.2%	13.0%	34.0%
Total	100.0%	100.0%	100.0%

Pearson Chi-Square Value = 8.846 Significance = p < 0.003

As can be seen in this table, dizziness is more common in the control group than the intervention group and it is significant at p< 0.003, which means there is just a 0.3% chance that the difference was an accidental finding.

Table 5 shows the percentage in each group with headache:

Table 5: HEADACHE by Control and Intervention groups

HEADACHE	Control group	Intervention group	Total
No	45.8%	60.9%	53.2%
Yes	54.2%	39.1%	46.8%
Total	100.0%	100.0%	100.0%

Pearson Chi-Square Value = 1.066 Significance = p < 0.302

As shown in this table, the control group had more headaches than the intervention group. However, it is not statistically significant. At p <0.302, there is a 30.2% chance that this difference happened by accident. In scientific research, it is not considered proven unless the significance is p<0.05. But since this sample was very small, it might be that there is a difference that would be significant if a larger were study was done.

Table 6 shows the percentage in each group with a complaint of feeling hot:

Table 6: Hot Feelings by Control and Intervention group

Hot Feelings	Control group	Intervention group	Total
No	54.2%	87.0%	70.2%
Yes	45.8%	8.7%	27.7%
Total	100.0%	100.0%	100.0%

Pearson Chi-Square Value = 8.698 Significance = p < 0.013

As can be seen in this table, hot feelings were more common in the control group than in the intervention group and it is significant at p<0.013, which means there is just only 1.3% chance that the difference was an accidental finding.

Table 7 shows the percentage in each group with nausea:

Table 7: NAUSEA by Control and Intervention Group

NAUSEA	Control group	Intervention group	Total
No	45.8%	95.7%	70.2%
Yes	54.2%	4.3%	29.8%
Total	100.0%	100.0%	100.0%

Pearson Chi-Square Value = 13.937 Significance = p <0 .000

As can be seen in this table, complaints of nausea were more common in the control group than the intervention group and it is significant at p<0.001, which means there almost no chance that the difference was an accidental finding.

Table 8 shows the percentage in each group with no appetite:

Table 8: No appetite by Control and Intervention Group

No appetite	Control group	Intervention group	Total
No	62.5%	95.7%	78.7%
Yes	37.5%	4.3%	21.3%
Total	100.0%	100.0%	100.0%

Pearson Chi-Square Value = 7.707 Significance = p<0.006

As can be seen in this table, complaints of no appetite were more common in the control group than the intervention group and it is significant at p <0.006, which means there is just only 0.6% chance that the difference was an accidental finding.

Table 9 shows the combined score of side effect for each group. 0 means no complaint of any side effect, 1 means one side effect was complained of, 2 means the same person complained of 2 different side effects, and so on.

Table 9: Side Effect Score by Control and Intervention Group

Side Effect Score	Control group	Intervention group	Total
.00	20.8%	56.5%	38.3%
1.00	8.3%	21.7%	14.9%
2.00	25.0%	17.4%	21.3%
3.00	12.5%	4.3%	8.5%
4.00	16.7%	.0%	8.5%
5.00	16.7%	.0%	8.5%
Total	100.0%	100.0%	100.0%
Mean Score	2.4583	0.6957	

Pearson Chi-Square Value = 14.226 Significance p <0.014

As can be seen in this table, the control group had much higher scores than the intervention group when all common side effects are considered. The control group had an average of more than 2 side effects per person, but the intervention group average was less than one. The difference is significant at p<0.014, which means there is only a 1.4% chance that the difference was an accidental finding.

VI. Discussion

Findings:

The average age of the control and intervention groups is almost the same with a difference of less than one year. The control group was a little shorter and weighed a little more on average than the intervention group, so the Body Mass Index (BMI) for the two groups is a little bit different but both are normal and the difference is small.

As can be seen in the table 2, many more women had side effects in the control group and this difference is statistically significant at probability (p) of .028. That means that there is only a 2.8% chance that the difference was an accidental finding. Table 8 shows that the control group had much higher combined scores than the intervention group when all common side effects are considered. The control group had an average of more than 2 side effects per person, but the intervention group average had less than one. The difference is significant at
$p < 0.014$, which means there is only a 1.4% chance that the difference was an accidental finding.

All five of the different side effects (nausea, dizziness, hot feelings, no appetite and headache) were more common in the control group than in the intervention group. Nausea and dizziness showed the greatest difference between groups: more than 40 percentage points, significant at $p<0.001$ for nausea and $p<0.003$ for dizziness , which means there is almost no chance that the difference was accidental. Hot feelings and no appetite were also very different (more than 30 percentage points) with significance of $p<0.006$ for no appetite and $p <0.013$ for hot feelings.

Although the control group had more headaches than the intervention group, it is not statistically significant. At $p < 0.302$, there is a 30.2% chance that this difference happened by accident. In scientific research, it is not considered proven unless the significance is $p<0.05$.

Limitations of the Data:

Because of the small sample size (47), only very large differences are statistically significant. For example, headache was more common in the control group than intervention group (54.2% against 39.1%) but with this sample size it cannot be said that it is significant. If the sample were larger, it might have been. However, other side effects had so much difference that even with the small sample size it was still significant.

The control group was a little bit better nourished than the intervention group (Mean BMI of 21.4 compared to 20.1). However this a small difference and both groups are in the normal range for mean BMI (normal BMI is 18.5 – 24.9). If the difference had any effect, it should have been to make the control group have less side effects, but the study showed they had more.

The sample is chosen from women who live in Phnom Penh only. Phnom Penh women have mostly better education, nutrition, and money than women who live in rural areas. Because they have better nutrition, the 25 mg of Vitamin B_6 that worked for them might or might not be the same for women in the countryside. The women in this study came to get family

planning from a clinic that could check their health, so they may be more educated than women who just buy the pill from the market. For this reason, the women in this study might have followed instructions better than other women would. There might be a different result if this study were done in a rural area where the women are uneducated and don't know much about taking care of their health.

VII. Conclusion

Vitamin B_6 25 mg a day reduces the following side effects in Phnom Penh women who take the conceptive pill: nausea, dizziness, hot feelings, and no appetite. More research with a larger sample is needed to see if it also helps reduce headaches. Phnom Penh clinics should give Vitamin B_6 to clients who use the conceptive pill, because it will reduce side effects so more women will use family planning, which will help the health of children and women in Cambodia. More research should be done in a rural area of Cambodia to see if the same amount of vitamin B_6 has the same result for rural women and if they will take it. A similar study should also be done with other hormonal contraceptives like Depo-Provera (injection) to see if vitamin B_6 helps reduce their side effects.

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