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Minor Side Effects, Tolerance and Discontinuation of Oral Contraception among Women in Rural Cambodia

Chivorn Var[1], Sheryl Keller[1], Rathavy Tung[2], Lu Yao[3] and Alessandra N. Bazzano[4*]

[1]Reproductive Health Association of Cambodia, No.14, St. 335, Phnom Penh, Cambodia.
[2]National Center for Maternal Child Health, Ministry of Health, Royal Government of Cambodia, No.31A, St.47, Phnom Penh, Cambodia.
[3]University of Minnesota, School of Public Health, 420 Delaware St. S.E., Minneapolis, MN 55455, USA.
[4]Tulane University, School of Public Health and Tropical Medicine, Department of Global Community Health and Behavioral Sciences, 1440 Canal St, New Orleans, LA 70112, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Author CV designed the study and monitored field work. Author SK wrote the study protocol, performed data analysis and wrote the study report. Author RT reviewed and commented on the study design and protocol. Author LY assisted with manuscript data analysis and presentation. Author ANB provided critical input to the interpretation of the data and drafted the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Contraceptive prevalence in Cambodia is relatively low, while maternal mortality, newborn mortality, and projected rates of abortion are high. Fears of side effects and health concerns appear to be the leading reasons for non-use of modern contraceptive methods. Data on contraceptive side effects was collected through a longitudinal study of women using oral contraception in rural Cambodia. Physical and perceived side effects were reported. One of the side effects reported, hot flashes, is not well documented. A perceived side effect which caused immediate discontinuation was that combined oral contraceptives cause fever and diarrhea in breastfed children. More common side effects

**Corresponding author: Email: abazzano@tulane.edu;*

were well tolerated. An opportunity exists to increase demand for contraception in Cambodia; understanding and addressing specific side effects which are particularly bothersome or which cause discontinuation, such as hot flashes, is an important step to improving the demand for contraception among women and families. This study sought to gather data on the specific side effects women were concerned about in order to find solutions which might encourage use and continuation.

Keywords: Combined oral contraceptive pill; adherence; Cambodia; side effects; rural health; contraception utilization; patient acceptance of health care.

1. INTRODUCTION

The modern method contraceptive prevalence rate among currently married women in Cambodia is only 35% [1], and while this reflects a substantial improvement over the recent past, it is still far short of the Cambodia Millennium Development Goal of 60% [2]. An estimated 25.1% of married Cambodian women had an unmet need for family planning (FP), and 30% of women reported having had an unplanned pregnancy in the years prior to the last Cambodia Demographic and Health Survey (CDHS) [1].

Fear of side effects and health concerns appear to be the leading reasons for non-use of contraception among Cambodian women with an unmet need for FP, as is the case in many low income countries [3].

Combined oral contraceptives (CoCs) are the predominant modern method of family planning in Cambodia; the second most common method is injectable contraception [1]. Pill use more than doubled between 2000 and 2005 and accounted for the majority of the overall increase in the modern Contraceptive Prevalence Rate during that period [4]. Data from the government's Health Information System (HIS) indicates that this trend has continued; in 2007, CoCs accounted for 52.3% of the modern method mix among clients served by a government facility [5]. Yet, there is an important segment of the population not served by this method.

In a 2005 survey of Cambodian women's perceptions of various family planning methods, the pill was rated highly in terms of ease of use, accessibility and cost. Perceived side effects, however, were a deterrent both to initial use and to continuation. Fifty-four percent of CoC discontinuers, and 70.1% of those discontinuing all methods (excluding those who wished to become pregnant), cited side effects as the reason for discontinuation; more than half of the women questioned stated that the main reason for not trying CoCs was fear of side effects [6]. Some side effects are more important to women than others. For example, menstrual cycle regulation is not a frequent complaint, so it seems unlikely that menstrual irregularities would be a major reason for avoiding the pill [3]. Health providers have reported that other complaints often do not respond to counseling, though, a situation which led the National Sexual and Reproductive Health Strategy 2006-2010 to include as one of its planned interventions the "development of medical protocols for alleviation of side effects associated with hormonal contraception" [7]. Studies of family planning among Cambodian women indicate that users and non-users are aware of side effects that may cause discontinuation for health reasons [8]. A related issue may be underlying nutritional status—nationally, 19% of women are underweight (BMI <18.5) and 44% anemic [1].

2. MATERIALS AND METHODS

The longitudinal study was nested within a quasi experimental investigation of Vitamin B6 for oral contraceptive side effects and was conducted from April 2009 – October 2010 in Kong Pisey Operational District (OD) of Kampong Speu Province, located in south-central Cambodia. It was overseen by four investigators, and two research assistants conducted field data collection under their supervision. The study site was selected because the province is typical of rural Cambodia, with a highly homogenous population of ethnic Khmer who are predominately Buddhist and employed in subsistence agriculture. In the study site, 30.1% of the population is below the poverty line, and 2005 birth control pill use rate was 11.5% [9].

Kong Pisey's population of 246,812 is served by 19 Health Centers (HC). All villages had trained village health volunteers who conducted community-based sales of oral contraceptives and condoms. Community-based Distribution (CBD) of contraceptives is conducted under the supervision of the HC, with HC supplied commodities, and is considered part of the formal public sector.

All new CoC acceptors served through the public sector (HC or CBD) from May 2009 onward were asked to participate provided they did not have a chronic disease and any prior CoC use was at least 6 months ago. Enrollment was voluntary with informed consent obtained. No women refused to participate, and a total of 1,022 were initially enrolled, 577 in the Vitamin B6 intervention group and 434 in the control group.

Eleven women were excluded for the following reasons: serious chronic disease identified at the first interview, pre-existing pregnancy, or move outside the study area. All participants provided informed consent, and the study was approved by Cambodia National Ethics Committee for Health Research.

The following data was collected at the time of initial enrollment into the study: age, parity, ownership of assets and housing material (to calculate socioeconomic status), education, weight and height, history of prior use of CoCs and, if any, reason for previous discontinuation. The initial enrollment forms were completed by the service providers who received two days training, including accurate measurement of weight and height and how to obtain informed consent. The information on the enrollment forms was then re-checked at the first follow up interview by the local research assistants employed. Weights and heights which fell outside the expected range based on national data from the CDHS, or which in combination produced a BMI outside expected range, were personally re-measured by the Research Assistants.

Women in the study were followed up periodically through August 2009. Follow up interviews were conducted at intervals which corresponded to approximately the 1st, third and sixth month of pill use for all women, since everyone was enrolled in the study for at least 6 months. Women who enrolled in the study before December 2009 also received a fourth final interview which corresponded to the 9th – 12th month of use depending on when the women enrolled relative to the end of the observation period. Women found at any point to have discontinued CoC use received no further interviews thereafter and are treated as having been enrolled in the study for the full year since their final use status is known.

The same questionnaire was used at all follow-up visits and consisted of questions about CoC use, nature of any side effects experienced and any measures taken to alleviate them,

and, if the woman was found to have discontinued use, the reasons for discontinuation. Quality Control was ensured through consistency checks of the completed questionnaires and spot re-interviews of 5-10% of each month's interviews by the Research Consultant.

Body Mass Index (BMI) as kg/m^2 was calculated from the heights and weights recorded at enrollment in the study. Socio-economic status (SES) was measured using a composite index that consisted of the composition of the home and ownership of assets by household members. SES was then divided into quintiles.

Descriptive statistics were used to identify the frequency with which various side effects were reported. Multivariate regressions were used to assess the relative contribution of various factors to the specific side effects and to key behaviors. Life table methodology was used to determine continuation rates by month of use, using the Survival Analysis function in SPSS.

3. RESULTS

Study respondents ranged in age from 17 to 47 years; the mean age was 28.8 years and the median, 28 years. As seen in Fig. 1, 17.4% had no education, 54.8% had an incomplete primary education, and only 27.8% had completed primary school. The mean number of years of schooling was 3.9 and the median, 4 years.

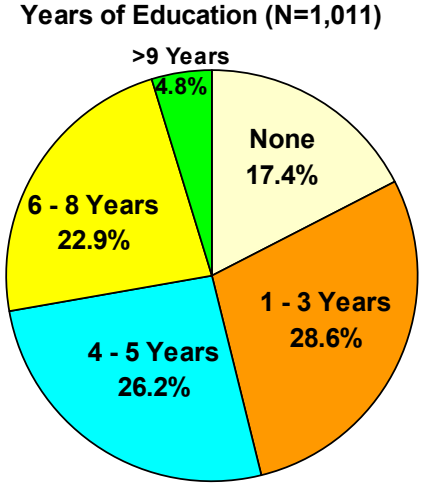

Fig. 1. Year of education (N=1,011) > 9 years

Almost all of the women had given birth to at least one child; the mean number of children ever born was 2.5 and the median was 2. More than a third of the women had 3 or more children.

Both education and parity see Fig. 2, varied by age, with younger women having fewer children and more years of schooling. Particularly striking is the higher level of education among women under 25 and the high parity of women aged 35 and over; both of these findings are consistent with nationwide trends.

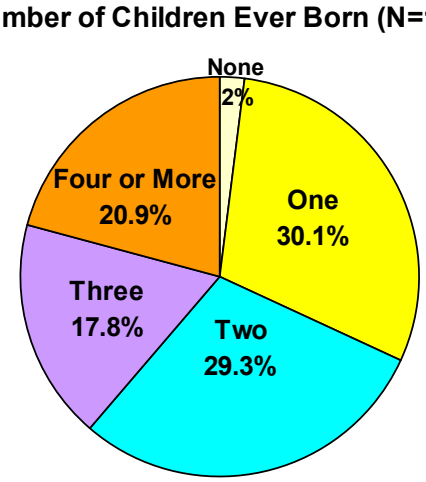

Fig. 2. Number of children ever born (n=1,011)

Women's weights ranged from 33.5kg (verified through re-check) to 73kg (likewise re-verified); the mean weight was 47.7kg and the median was 47.0kg. Heights ranged from 140cm to 170cm with a mean of 152.8cm and a median of 150.0cm.

Table 1. Mean number of children ever born and years of schooling by age group

Age group	Mean number of children	Mean years of education
under 25 (N=250)	1.25	5.00
25 - 29 (N=398)	2.01	3.88
30 - 34 (N=168)	3.13	3.20
35 and over (N=195)	4.50	3.22

21% of the women were undernourished as defined by a BMI of less than 18.5. Interestingly, BMI had only a small positive correlation to socioeconomic status (r= .068, p = .03), and parity had no effect when age was controlled for. Women under the age of 30 were significantly more likely to be underweight than older women, probably because of the residual effect of the adolescent growth spurt and the effects of child-bearing and lactation.

3.1 Type of Side Effects Reported

In order to avoid the effect of suggestion, questions about side effects were asked in an open-ended manner; although a number of possible responses were pre-coded, the list was not read to the women. In total, 73.9% of women complained of one or more perceived side effects at some point during follow-up. Problems reported by more than 10% of the women were as follows:

- Nausea (with or without vomiting)
- Dizziness
- Headache
- Hot flashes
- Depression
- Menstrual changes

Dizziness (Khmer: *velmuk* or *ting tong*) posed the greatest challenge to analysis. It was often associated with either nausea or headache; indeed, almost half of all dizziness occurred in conjunction with one of these problems. Among women reporting both dizziness and nausea at the first follow-up visit, the status of both problems was the same at the subsequent follow-up in all but 12.8% of cases, i.e. either both problems had resolved or both had continued. A similar pattern was seen between the second and third follow-up.

Among women reporting both dizziness and headache, the same thing occurred: in 88% of cases either both problems resolved or both problems continued at the next visit; rarely did one symptom continue in the absence of the other. Headache accompanied by dizziness may reflect hypertension or migraine; significant hypertension was an incidental finding in several older women.

However, there were cases of dizziness which were not accompanied by either headache or nausea. Hot flashes were not found to have a significant association. After experimentation with several alternative approaches to analysis it was found that the most robust results were obtained by treating dizziness as a discrete side effect if it occurred in the absence of nausea or headache, but not when it occurred in tandem with either of those problems.

The following problems were reported by 1–5% of women at some point: weight gain/weight loss, myalgia, abdominal pain/cramps, vaginal discharge, loss of appetite, breast tenderness/swelling or mass, gastritis, sleep disturbance, illness in a breast-feeding child, and fever/respiratory infection.

With the exception of the last two complaints listed, these are also all known CoC side effects. For the purposes of this analysis, loss of appetite was included with nausea and vomiting on the assumption that it represented a milder end of the same spectrum. Weight loss most often occurred in conjunction with nausea/vomiting/loss of appetite, in which case it was not considered a separate symptom but rather an outcome of these.

Other problems, reported by less than 1% of the women, were insufficient breast milk, a bad taste in the mouth, visual disturbance, chest pain/trouble breathing, trembling, numbness in the extremities and cervicitis/endometritis.

In all but one case, visual disturbances were accompanied by headache and thus may have been due either to hypertension or migraine. All women reporting chest pain/trouble breathing also reported headache and most also reported dizziness; these may also have been hypertensive. Early in the study, a routine quality spot-check by SK (a clinician) identified severe hypertension in a 40 year old woman; following this, interviewers were instructed to refer any case of severe headache in women over age 35 and 4 similar cases were found. As the study was not designed to detect hypertension, it is quite likely further cases slipped through undetected. During final analysis, another 4 cases were found which appeared suggestive of hypertension, e.g. severe headache accompanied by at least one of the following: dizziness, shortness of breath, or visual disturbance, particularly in women aged 35 and above. CBD Agents in Cambodia are not equipped or trained to check blood pressure, and even when CoCs are obtained from a health facility the blood pressure is typically not assessed.

3.2 Prevalence of Specific Side Effects over Time

Specific side effects varied in the point at which they were likely to be reported, their duration, and how likely women were to discontinue use because of them. This section describes findings by interview sequence, i.e. at the first, second, third and (where applicable) fourth follow-up interviews. These approximately correspond to 1, 3, 6 and 9-12 months of use.

3.2.1 First month of use

At the first follow-up visit, conducted about one month after the start of CoC use (median = 34 days, mean=41.3 days), 55% of the women had one or more complaints they attributed to CoCs. Fig. 3 disaggregates the participants reporting a side effect, while Table 2 illustrates overall reporting of side effects by type.

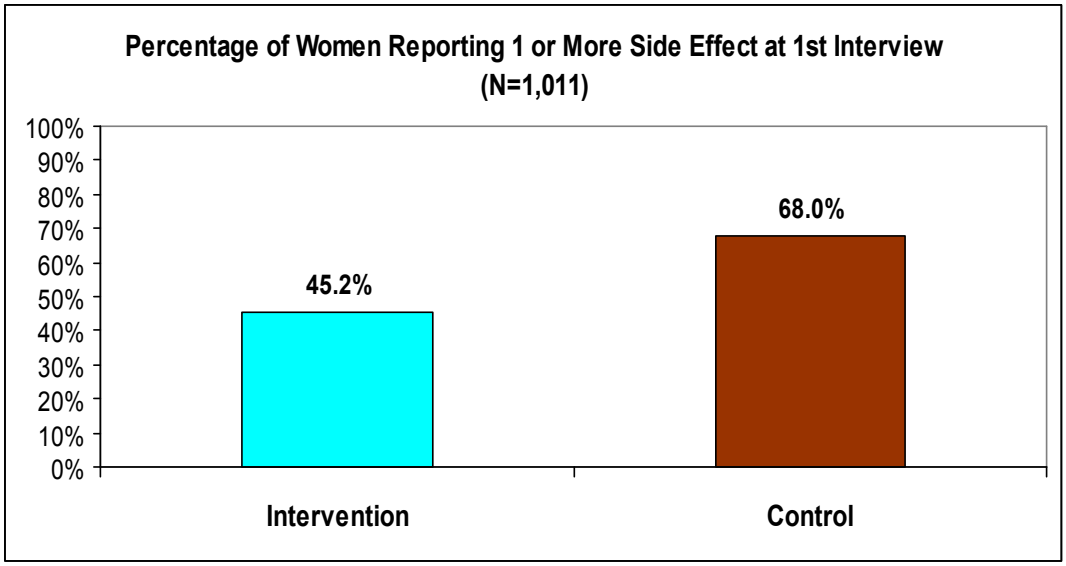

Fig. 3. Women reporting side effects at 1st interview
Chi Sq=51.7 p=.000

The following table shows the side effects reported at the first follow up, i.e. after approximately one month of CoC use. The total exceeds the percentage with any complaint as some women reported more than one problem.

Table 2. Side effects reported at first follow-up (N=1,011)

Complaint	% Women
Nausea/no appetite (with or without vomiting, weight loss, dizziness)	30.0%
Headache (with or without dizziness)	14.9%
Hot Flash	14.4%
Depression	7.9%
Dizziness (not associated with nausea or headache)	4.4%
Menstrual Change	3.5%
Weight gain	1.6%
Baby sick*	1.1%

**the woman ascribed a breast-fed child's illness (e.g. fever or diarrhea) to her CoC use*

In addition to the above the following were reported by 1% or less of the women: fever/respiratory infection, breast tenderness/swelling, gastritis, myalgia, sleep disturbance, weight loss (in the absence of nausea/vomiting or loss of appetite), an unpleasant taste in the mouth and vaginal discharge.

Fifty-four women (5.3% of the total) had stopped use due to side effect(s) by the time of the first interview, and 13 women were found to have discontinued for other reasons. The mean duration of use before discontinuation was 27 days and the median, 24.

The following Table 3 shows, as a percentage of women reporting a particular complaint at the first visit, the percentage that had discontinued use on those grounds.

Table 3. Discontinuation as a % of women experiencing the side effect, 1st visit

Side effect	% Discontinuing as a result
Baby sick (N= 11)	100.0%
Dizziness (without nausea or HA) (N= 44)	20.5%
Hot Flashes (N= 146)	13.0%
Menstrual Change (n=35)	11.4%
Headache (with or without dizziness) (N= 151)	7.9%
Nausea/no appetite (with or without vomiting, weight loss, dizziness) (N= 303)	6.6%
Depression (N= 80)	1.3%

Side effects experienced by the woman herself (as opposed to a problem in her child ascribed to pill use) were generally tolerated during the first month. Tolerance for nausea/vomiting/loss of appetite–the most commonly experienced side effect–was especially high, with only 6.6% of women reporting this problem choosing to discontinue because of it within the first month of use. Tolerance for headache was also quite high. Hot flashes and dizziness were more likely to lead to early discontinuation, although a majority of women still continued use.

3.2.2 Third month of use

A second interview was conducted approximately 3 months after the start of pill use. The mean duration of use at the second interview was 120 days and the median, 95 days. At this point 7 women successfully interviewed at the one month mark were lost to follow-up due to having moved out of the province or migrated abroad for work: 4 in the intervention group and 3 in the control. Together with 67 women who had discontinued use at the first follow-up (54 due to side effects and 13 for other reasons), this left 937 women who were successfully

interviewed, and a total of 1,004 women whose use status was known (those successfully interviewed and those known to have already discontinued).

Among the 937 women interviewed, 37% reported any side effect. Even adjusting for the 54 women who discontinued due to side effects at the first follow-up (i.e. adding them to both numerator and denominator), there is still a significant decrease in the percentage of women reporting any side effect at the first follow-up.

This is almost entirely due to a large decrease in the percentage reporting nausea/no appetite; as shown in Table 4, changes in the prevalence of other complaints were minimal.

In addition to the above, the following were reported by less than 1% of women: myalgia, vaginal discharge, gastritis, breast tenderness, sleep disturbance, abdominal pain/cramps and insufficient breast milk.

As shown below, differences in the prevalence of reported side effects between intervention and control groups remain highly significant, although the magnitude is lower than it was at the first month. This is due to a disproportional decrease in the percentage of women complaining of nausea/loss of appetite, the side effect for which the greatest difference was seen in women receiving B6 supplementation.

Table 4. Side effects reported at second follow-up (N=936*)

Complaint	% Women
Nausea/no appetite (with or without vomiting, weight loss, dizziness)	9.1%
Hot Flash	9.0%
Headache (with or without dizziness)	8.1%
Depression	5.8%
Dizziness (without nausea or HA)	4.8%
Menstrual Change	4.8%
Weight loss (without nausea/vomiting or loss of appetite)	1.8%
Fever/respiratory infection	1.6%
Baby sick	1.4%
Weight gain	1.2%

** Excludes 67 women who discontinued use at the first follow up, 7 women lost to follow-up and 1 case of missing data.*

A total of 136 women were found to have discontinued CoC use at the second follow-up. In contrast to the first follow-up, at which time the majority of discontinuations were due to perceived side effects, almost half of these were for other reasons: 18 women discontinued use in order to change to a longer-acting method, 17 decided to have a baby, 3 found they were pregnant, 14 were no longer having sex (temporary or permanent separation from spouse), 4 could not remember to take the pill, 3 reported they had been too busy working in the rice field to find time to buy pills, one had no money with which to buy, and one reported stopping because her husband objected for unspecified reasons.

Sixty-nine women discontinued due to side effects, and another 6 women discontinued for health-related issues: they were receiving treatment for an unrelated medical problem and were afraid to take CoCs at the same time. In some cases the provider had advised this and in others it was the woman's own decision. None of the cases involved medication contraindicated in conjunction with CoCs, i.e. the discontinuation was unnecessary.

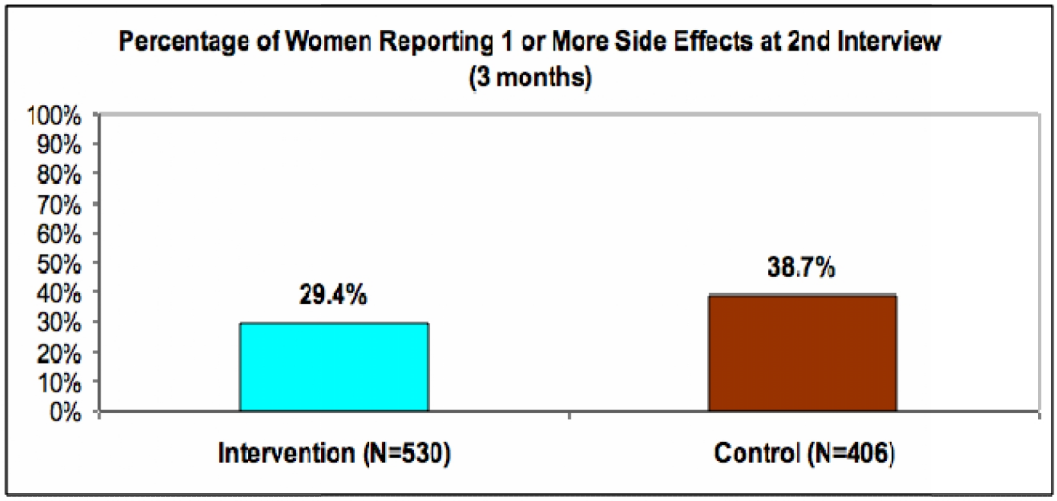

Fig. 4. Women reporting side effects at 2nd interview
Chi Sq=17.5 p=.001

The mean duration of use among women found to have discontinued due to side effects at the second visit was 103 days and the median 83 days; the mean is skewed by a few cases whose interviews were unusually delayed due to difficulty locating them.

As was true at the first follow-up, all women who attributed a child's illness to their pill use discontinued, while a majority of women with other complaints continued use. However, the percentage of women experiencing various other side effects who chose to stop as a result was higher than it had been at the first follow up.

Table 5. Discontinuation due to specific side effects as a percentage of women experiencing that side effect, 2nd visit

Side effect	% Discontinuing as a result
Baby sick (N= 4)	100.0%
Hot Flash (N= 33)	31.0%
Dizziness (without nausea/loss of appetite) (N= 13)	22.2%
Menstrual Change (N= 14)	20.0%
Headache (with or without dizziness) (N=21)	19.7%
Nausea/no appetite (with or without weight loss, vomiting, dizziness) (N= 24)	16.5%
Depression (N= 13)	16.7%

3.2.3 Sixth month of use

A third follow-up interview was conducted approximately 6 months after the onset of CoC use. At this point an additional 8 women (for a cumulative total of 15) could not be located. In 7 cases this was due to moving outside the study area, while one woman developed a serious mental illness and was taken to an unknown location for extended treatment by her family. In addition, one woman in the Intervention group was dropped from the study after the second interview due to a sustained, involuntary disruption of B6 supply.

A total of 793 women were thus interviewed for a third time: 1,011 minus those who discontinued at the first and second follow-ups and 16 lost to follow up/excluded. The mean duration between onset of CoC use and the third interview was 194 days and the median, 183 days.

In 6 cases the third interview was obtained retrospectively from information provided in the fourth interview from a woman who stopped CoC use after month 9 for reasons other than side effects. In these cases only use status was recorded for the third visit as recall about side effects was considered unreliable. The incidence of reported side effects at this stage was not noticeably different from that seen at 3 months: 31.4% of the women had one or more complaints.

Table 6. Side effects reported at third follow-up (N=787*)

Complaint	% Women
Hot flash	8.8%
Nausea/no appetite (with or without vomiting, weight loss, dizziness)	7.8%
Headache (with or without dizziness)	5.6%
Menstrual change	5.6%
Dizziness (without nausea/vomiting or loss of appetite)	4.6%
Depression	4.3%
Myalgia	1.4%
Baby sick	1.4%
Gastritis	1.4%
Weight loss (without nausea/vomiting or loss of appetite)	1.3%
Weight gain	1.1%

** Excludes 203 women who discontinued use at the first or second follow up, 15 women lost to follow-up, 1 woman excluded due to loss of B6 supply and 6 cases of missing data*

Side effects reported by 1% or less of users at the third follow-up were: sleep disturbance, vaginal discharge, an unpleasant taste in the mouth, breast tenderness/lumps, and abdominal pain/ cramps

Ninety-five women were found to have discontinued use at the 3rd follow up, 47 of them because of perceived side effects and 48 for other reasons: 11 had decided to have a child, 2 found they were pregnant, 12 were not having sex, 8 changed to another method for convenience (IUD and injection), 3 were unable to remember to take the pill, 5 were "too busy" to buy the pill, and 3 had no source of supply (the CBD Agent ran out of stock). In addition, as at the second follow-up, some women (4) discontinued because they had an unrelated illness and were afraid to combine CoCs with other medications.

Also in keeping with the first and second follow-up, a number of women (11) ascribed illness in a breast-fed child to their CoC use and all of these discontinued; in fact, this was second only to hot flashes as a reason for discontinuation at the 6 month mark.

Table 7 shows the proportion of women who discontinued due to a side effect as a percentage of all women with that side effect. Tolerance for most side effects was similar at 6 months as at 3, with the exception of a greater tendency to discontinue in the face of depression.

Table 7. Discontinuation due to specific side effects as a percentage of women experiencing that side effect, 6 month follow-up

Side effect	% Discontinuing as a result
Baby sick (N= 3)	100.0%
Depression (N= 13)	29.4%
Hot Flash (N= 22)	26.1%
Headache (with or without dizziness) (N= 13)	22.7%
Menstrual Change (N= 13)	22.7%
Nausea/no appetite (with or without vomiting, weight loss, dizziness) (N= 8)	13.1%
Dizziness (not accompanied by nausea or HA) (N= 5)	8.3%

3.2.4 Final visit (9–12 months)

Women who enrolled prior to mid November 2009 received a fourth and final follow up visit. A total of 646 women received a fourth interview, while for 32 women who enrolled less than 9 months before the end of the study period, the third follow up served as the final. The fourth interview was conducted a mean of 348 days after initiation of pill use and a median of 365 days.

The percentage of women reporting one or more side effects was essentially unchanged in comparison to months 3 and 6, with 31.4% reporting one or more side effects. Indeed, factoring in the cumulative number of women who had stopped due to a side effect, it appears that a very slight increase occurred both between months 3 and 6 and again between months 6 and 9-12.

Table 8. Side effects reported at fourth follow-up (N=654*)

Complaint	% Women
Hot flash	9.3%
Headache (with or without dizziness)	7.0%
Depression	5.9%
Nausea/no appetite (with or without vomiting, weight loss, dizziness)	5.3%
Menstrual change	4.3%
Dizziness (without nausea or HA)	3.4%
Weight gain	3.4%
Other unrelated	3.0%
Myalgia	2.5%
Vaginal discharge	2.0%
Weight loss (without nausea/vomiting or loss of appetite)	1.4%
Abdominal pain/cramps	1.4%
Gastritis	1.1%

While the overall percentage of women reporting a side effect at 9-12 months use was similar to that at 3 and 6 months, the type of side effect complaint differed. Nausea/loss of appetite, which had steadily decreased in prominence after the first month, was now reported by only 5.3% of the women while the prevalence of hot flashes was actually a bit higher than at months 3 and 6, and complaints of weight gain and of vaginal discharge had also increased.

Illness in a child, sleep disturbance and breast tenderness or mass were reported by less than 0.5% of users. Among the women reporting a breast problem, 3 had actual masses and were advised to change to a non-hormonal form of contraception. One of the masses resolved after stopping CoCs and was thus presumably a functional cyst while the other 2 masses persisted. These women were brought to Phnom Penh for evaluation and the masses found to be benign.

A total of 96 women were found to have newly discontinued use at the time of the 4th interview, see Table 9, and 36 of these were due to side effects with the remaining 60 for other reasons: e.g. desire to have a child (21), not having sex or "too old to get pregnant" (14), change to IUD or injection for reasons of convenience (9). 2 women had become pregnant and 9 women stopped due to concern about combining CoC use with treatment for an unrelated medical problem – making a cumulative total of 20 women (2.0%) who stopped for that reason. In addition, 3 women stopped because they could not remember to take the pill, 1 had a supply problem, and 1 woman stopped out of fear that using for "too long" would be harmful to her health. Eleven of the above discontinuations (including 4 due to side effects) occurred more than 365 days after enrollment.

Below, Table 10 shows the percentage of women experiencing a side effect problem related to the use of COCs for the entire period of the study.

Table 9. Discontinuation due to specific side effects as a percentage of women experiencing that side effect, 4th visit

Side effect	% Discontinuing as a result
Baby Sick (N = 1)	100.0%
Hot Flash (N= 20)	32.3%
Nausea/no appetite (with or without vomiting, weight loss, dizziness) (N=8)	23.5%
Dizziness (without nausea or HA) (N= 5)	22.7%
Menstrual Change (N= 4)	14.3%
Depression (N= 5)	13.2%
Headache (N= 5)	10.9%

Table 10. Percentage of women reporting specific side effects at any point in time (N=1,011)

Complaint	% Women
Nausea/no appetite (with or without vomiting, dizziness, weight loss)	36.3%
Hot Flash	26.1%
Headache (with or without dizziness)	23.9%
Depression	15.2%
Menstrual Change	12.5%
Dizziness (without nausea or HA)	11.9%
Weight gain	5.0%
Fever/URI	4.1%
Baby sick	3.9%
Myalgia	3.7%
Gastritis	2.9%
Vaginal discharge	2.6%
Weight loss (without nausea/vomiting or loss of appetite)	2.4%

In addition to the above noted side effects, less than 2% of women reported the following problems at any point in time during the study:

- Abdominal pain/ cramps
- Sleep disturbance
- Bad taste in the mouth
- Breast tenderness or mass
- Visual disturbance
- Chest pain/trouble breathing
- Trembling
- Numb extremities

As the Fig. 5 illustrates, the prevalence of nausea substantially decreases with time, but decreases in hot flashes and headache are modest (and, in the case of hot flashes, offset by women who had already discontinued due to that complaint). The prevalence of dizziness, depression and menstrual complaints are fairly stable.

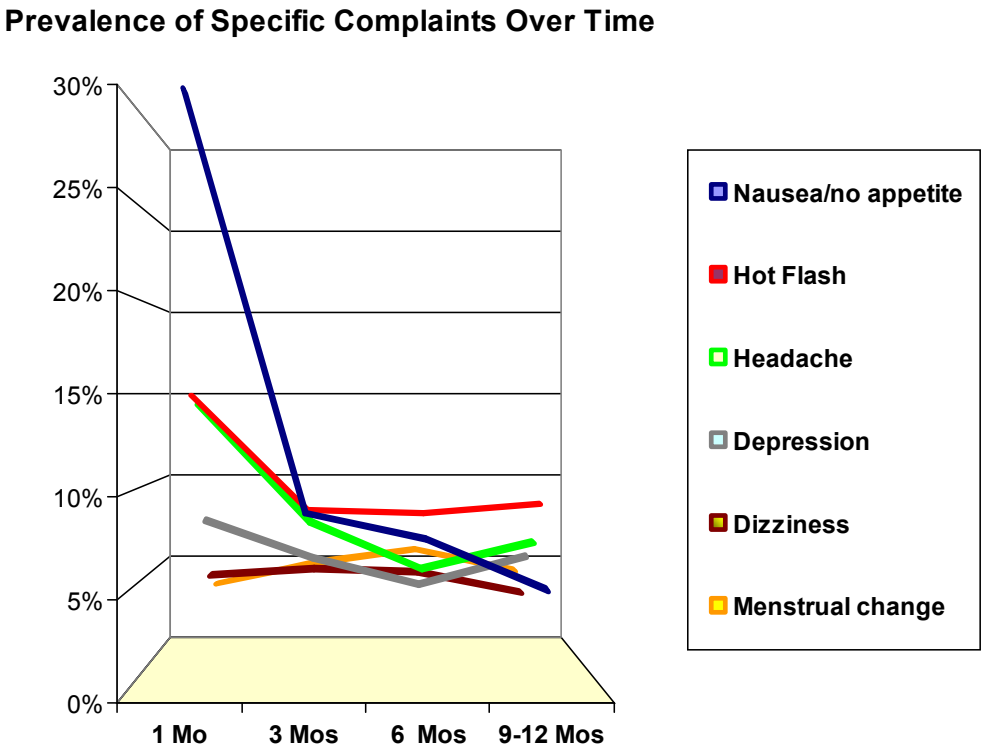

Fig. 5. Prevalence of specific Complaints over time

A total of 206 of the women enrolled in the study discontinued use due to perceived side effects. Included among them are 39 women who attributed illness in their child (usually fever or diarrhea) to CoC use; 31 of these had no other complaint and thus are considered to have stopped due to wrongly ascribing to the pill a problem which cannot have been related to it, as are 2 other women with complaints not plausibly connected to CoC use (fever, respiratory infection). In addition, 20 women discontinued due to fear that it was unsafe to

combine CoCs with other medications and 2 discontinued because of fear that using CoCs for "too long" would be harmful or cause sterility. Inclusive of these 22 cases, 228 women discontinued because of side effects/health concerns as follows:

- 173 women had complaints that are either known side effects of hormonal contraception or plausibly linked to it. 169 of these discontinued within a year of use while 4 did so after an interval of more than a year.

- 55 women discontinued due to unfounded health concerns, chiefly the misperception that CoCs can cause fever or diarrhea in a breast-feeding child or that it is not safe to take CoC while under treatment for unrelated illnesses. 2 of these discontinuations occurred after more than a year of use while the rest occurred within a year.

Fig. 6 summarizes the use status of women in the study over time. It should be noted that these times are approximate and reflect the average duration of use among women at the 1st, 2nd, third and final follow-up interview.

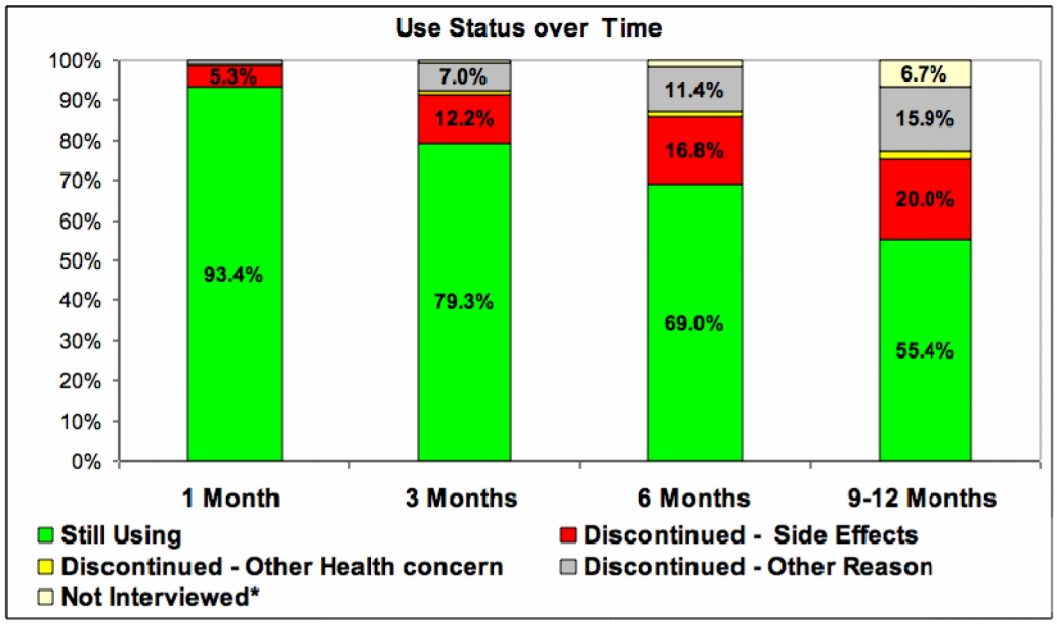

Fig. 6. Use and discontinuation status of women during study

Note: "not interviewed"=lost to follow up , deceased or (at 9-12 months) women who were enrolled for less than 9 months time

The preceding figures, as well as the continuation rate calculations treat the 11 women who discontinued use after more than 365 days as "still using". However, these cases are included in analyses of causes of discontinuation.

In addition to having different patterns of onset and duration, side effects differ markedly in the likelihood that they would lead to discontinuation. Women experiencing hot flashes were more than twice as likely to stop using the method for that reason as women reporting

nausea, headache, menstrual changes or depression. In fact, nausea was exceptionally well tolerated.

Although only 3.9% of women reported that they believed their baby had become ill as a result of their CoC use, all who did so discontinued as a result. Hence this misconception, while not widespread, accounted for a disproportionate amount of discontinuation.

Fig. 7 shows the number of women who discontinued due to a specific side effect as a percentage of the total ever reporting that problem. It should be noted, however, that half of the women cited more than one side effect as the reason for discontinuation and these may not have been equally influential.

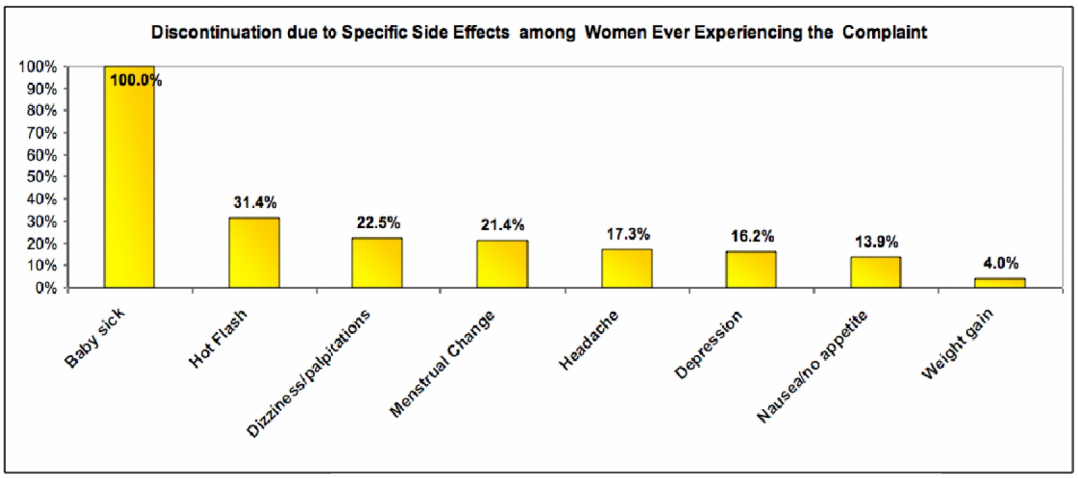

Fig. 7. Discontinuation among women ever reporting a side effect

Denominators

Nausea/no appetite	**367**
Headache	242
Hot flash	264
Depression	154
Dizziness	120
Menstrual change	123
Baby sick	39
Weight gain	51

Fig. 8 shows the percentage of women who discontinued due, at least in part, to a specific side effect. This captures the effects both of how common the complaint was and how well it was tolerated by those who had it.

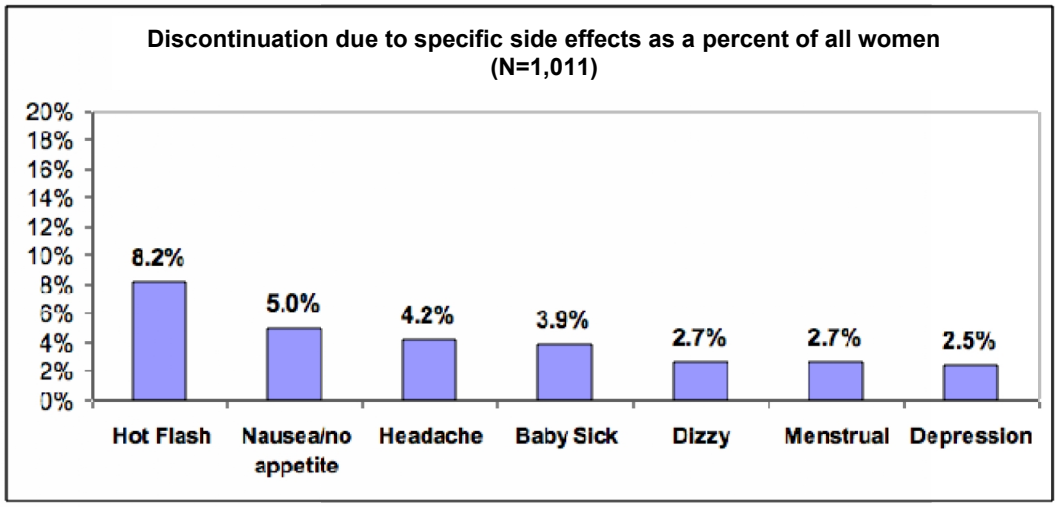

Fig. 8. Percent of all women who discontinued due to a specific side effect.

Since women often mentioned several different side effects as the reason for discontinuation, a binary logistical regression was done to isolate the respective contribution of different side effects to the likelihood that a woman would discontinue use. For this purpose, the dependent variable was discontinuation due to a likely CoC side effect, i.e. excluding discontinuation because of illness in a child (31 cases) or fever/respiratory infection (2 cases) ascribed to CoCs.

4. DISCUSSION

As shown in our data, hot flashes play the greatest role in discontinuation due to side effects despite occurring less often than nausea/loss of appetite, and generally menstrual complaints were not reported as a prominent cause of discontinuation in this population. Dizziness unassociated with nausea was also highly predictive, more than doubling the odds of discontinuation. Headache alone had no impact, but headache accompanied by dizziness had a small effect. Nausea and menstrual complaints were not significant, although they slightly improved the fit of the model. Respondent background characteristics such as age, SES and education had minimal effect.

Cultural factors may account for the comparative unimportance of menstrual complaints. Possible explanations for why hot flashes and dizziness were so much more likely to lead to discontinuation than were nausea and headache may include (1) the fact that these problems did not tend to improve much with time and (2) the efficacy of home remedies/coping strategies. A significant proportion of women suffering from nausea/loss of appetite employed home remedies which were generally effective in enabling them to wait out this problem, and women with simple headache often obtained relief from paracetemol. This was not the case with hot flashes and dizziness; home remedies were both less prevalently employed and less effective.

With the exception of hot flashes, all of these are well known side effects of combined oral contraceptives [10]. Hot flashes are a known effect of fluctuations in estrogen levels (as experienced during menopause/peri-menopause) and also a known effect of synthetic

progestin, but are not listed as a side effect of contraceptive pills in any of the manufacturer product data sheets reviewed nor mentioned in any of the internationally accepted contraceptive reference manuals [11]. CoCs contain only a low level of synthetic progestin. Likewise the comparatively small dose of estrogen in CoCs (30mcg of ethinyl estradiol in this instance) is not usually reported to produce this effect. However, hot flashes were not only reported by many women in this survey but are documented in internal government studies of Cambodian women and are widely reported by service providers throughout the country. Data on the type and prevalence of minor side effects of CoCs are predominately derived from studies in developed countries, and there is a scarcity of quantitative data from developing countries. One of the few such studies, a 2001 survey in Bangladesh, found that 10% of CoC users in that country also reported what was termed a "burning sensation" [10].

Since Cambodian health beliefs include the Chinese concept of "hot" and "cold", the possibility of confusion between actual experience of a hot flash and a belief that the body was hot was investigated through extensive discussions with women reporting this complaint, service providers and the research assistants. These confirmed that what was being reported was an actual sensation of extreme heat; women described being overcome with a sudden feeling of burning up from within and being drenched in sweat, sometimes followed by a chill when the heat sensation subsided–a scenario familiar to many menopausal women. Reported attempts at mitigation included women reported taking extra baths, fanning themselves, taking paracetemol and lying under wet cloths in attempts to get relief.

Understanding of psychological conditions is very limited in rural Cambodia, and women in different cultures vary in how they describe the subjective experience of them. In this study, the complaints assumed to equate to depression were expressed as an unusual exhaustion/fatigue, a "heavy" sensation in the body and/or a feeling of not wanting to do anything or to get out of bed. Some errors of both inclusion and omission are likely; as discussed below, other types of psychosomatic complaints and reports of sleep disturbance (either insomnia or excessive sleepiness) were not categorized as depression due to being insufficiently specific, and, of course, some complaints of unusual fatigue may have had other causes.

Our findings contrast somewhat with a recent multi-country study of women's experiences with oral contraception indicated that the most common side effects reported when requesting another method of contraception were breast tenderness, nausea, edema, headaches, cramps, acne and irritability. Hot flashes were not mentioned by participants from any of the study's country populations [12] nor were they mentioned by women in another multi country study which found the following side effects associated with discontinuation: nausea, bleeding, breast tenderness, mood changes and weight gain [13]. A longitudinal study among women in Sweden by Larrson and colleagues found menstrual bleeding disorders, weight gain and mental side effects were the most common reasons for discontinuation of oral contraceptives [14]. Other sources in the literature point out the possibility that side effects may be misattributed to oral contraceptives due to the "nocebo" effect [15].

An important limitation of this study was that all data were based on self-report potentially creating bias. In order to minimize measurement error, we extensively trained all the interviewers and other research coordinators and controlled the process, however it is possible that results were over or underreported. Another limitation is that many women gave more than one side effect as reason for discontinuation and their influences may not

have been equal. Finally, we report on side effects noted by women using combined oral contraceptives, but not one particular formulation or brand of contraception, thereby making it difficult to ascertain the components which might contribute to the side effects mentioned. As noted recently by Bitzer, the overall side effect profile of each combined hormonal contraceptive depends on the amount of each hormone contained within the formulation, as well as the specific type of progestin used; and the side effects of the progestin component are often attenuated by the estrogenic component. However, irregular bleeding, amenorrhea, breast tenderness, abdominal bloating, headache and nausea are the common side effects of all oral contraceptives [16]. A Cochrane systematic review found that discontinuation and side effects were reported across all types of combined oral contraceptives, regardless of the type of progestogens including in the formulation [17].

One systematic review studied negative attitudes regarding oral contraception across countries and found that negative feeling largely stems from concerns about health risks and side effects, and suggests that these may be able to be counteracted with appropriated counseling and information [18].

5. CONCLUSION

Our findings differ somewhat from what has been reported in other studies, and highlight the importance of country-specific assessments of contraceptive use and requirements. Even where the side effects experienced are similar, the extent to which they are tolerated may vary considerably. A recent study has noted that routine counseling may be as effective as intensive counseling in addressing new user concerns [19]. In order to ensure that the contraceptive needs of women and families are met in Cambodia and other settings with low uptake of contraception it will be necessary to continue to gather more data on the fear of side effects and to find solutions, through counseling or other means, which may improve the uptake of these effective methods.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this study and accompanying data.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the Cambodian National Ethics Committee for Health Research and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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