นิพนธ์ต้นฉบับ

ความไม่สอดคล้องกันของเอกสารกำกับยาสำหรับผู้ใช้ยารับประทานคุมกำเนิดที่มีจำหน่ายในประเทศไทยจำนวน 24 ผลิตภัณฑ์

สุมามาศ ระเบียบโอษฐ์, สุภาวดี เพชรพรหม และ จุราพร พงศ์เวชรักษ์ *

คณะเภสัชศาสตร์ มหาวิทยาลัยสงขลานครินทร์ หาดใหญ่ สงขลา 90112

* *ผู้เขียนที่สามารถติดต่อได้ โทรศัพท์: 074288871-3, โทรสาร: 074428222, ที่อยู่อิเลคโทรนิค: pjurapor@pharmacy.psu.ac.th*

บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อตรวจสอบและเปรียบเทียบข้อมูลยาในเอกสารกำกับยาของยารับประทานคุมกำเนิดที่มีจำหน่ายในประเทศไทย รายการผลิตภัณฑ์ยาที่มีจำหน่ายในประเทศไทย ได้จากกองควบคุมยา สำนักงานคณะกรรมการอาหารและยา เอกสารกำกับยาของยารับประทานคุมกำเนิดจำนวน 24 ผลิตภัณฑ์ ได้ถูกทบทวนเปรียบเทียบกัน แสดงในรูปตารางและใช้สถิติเชิงพรรณนาคือความถี่และร้อยละ เอกสารกำกับยาของทุกผลิตภัณฑ์ บอกวิธีการเริ่มรับประทานยาอย่างน้อย 1 วิธี น้อยกว่าร้อยละ 50 ให้คำแนะนำการปฏิบัติเมื่อลืมรับประทานยาตั้งแต่สองเม็ดขึ้นไป เอกสารกำกับยาส่วนใหญ่ ให้ข้อมูลเกี่ยวกับสภาวะทางคลินิกบางอย่าง ว่าเป็นข้อห้ามใช้ยารับประทานคุมกำเนิด ซึ่งขัดแย้งกับเกณฑ์ขององค์การอนามัยโลกที่แนะนำให้ใช้ยาได้ในสภาวะดังกล่าว ร้อยละ 50 มีข้อความสำหรับข้อควรระวังซึ่งบังคับให้มีและเฉพาะเจาะจงสำหรับยารับประทานชนิดฮอร์โมนรวม เอกสารกำกับยาส่วนใหญ่บอกผลไม่พึงประสงค์จากการใช้ยาที่พบได้บ่อย แต่ผลระยะสั้นในการรบกวนรอบเดือน มีกล่าวในเอกสารกำกับยาน้อยกว่าร้อยละ 25 เอกสารกำกับยาจำนวนน้อย ให้ข้อมูลเกี่ยวกับประโยชน์อย่างอื่นต่อสุขภาพที่นอกเหนือจากการคุมกำเนิด น้อยกว่าร้อยละ 50 มีข้อมูลเกี่ยวกับอาการเตือนเกี่ยวกับผลไม่พึงประสงค์ที่รุนแรงของยา ผลิตภัณฑ์จากบริษัทผู้ผลิตเดียวกันของต่างประเทศ มีเอกสารกำกับยาที่คล้ายคลึงกันในเนื้อหาและปริมาณ ซึ่งยาวกว่าเอกสารกำกับยาของผลิตภัณฑ์ที่ผลิตโดยบริษัทยาในประเทศ สรุปว่ามีความไม่สอดคล้องกันและไม่เพียงพอของข้อมูลในเอกสารกำกับยาของยารับประทานคุมกำเนิดที่จำหน่ายในประเทศไทย ดังนั้น ผู้ใช้ยารับประทานคุมกำเนิดชื่อการค้าต่างกันอาจได้ประโยชน์ไม่เท่าเทียมกัน จึงควรมีแนวปฏิบัติเฉพาะสำหรับการผลิตเอกสารกำกับยาของผลิตภัณฑ์ยารับประทานคุมกำเนิดที่ยึดผู้ใช้เป็นหลัก

กุญแจคำ

ยารับประทานคุมกำเนิด, เอกสารกำกับยาสำหรับผู้ใช้

Original Article

Discrepancies of Patient Package Inserts of 24 Brand Name Oral Contraceptive Pill Products in Thailand

Sumamas Rabeab-oat, Supawadee Petch-phrom and Juraporn Pongwecharak

Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hatyai, Songkhla 90112
** Corresponding author. Tel: +66 74 288871-3, Fax: +66 74 428222, E-mail address: pjurapor@pharmacy.psu.ac.th*

Abstract

The study was to examine and compare drug information provided in package inserts of oral contraceptive products marketed in Thailand. List of the products currently marketed in Thailand was obtained from Drug Control Division, Food and Drug Administration. Package inserts of 24 oral contraceptive products were reviewed against each other and the comparison was tabulated. Descriptive statistics, i.e., frequency and percentage were used. All package inserts provided at least one method for beginning the pill. Less than a half gave an advice on how to do when missing two or more pills. Some clinical conditions, being contrary to WHO eligibility criteria for the pill use, were presented as a contraindication in up to a third of the products. Compulsory precautionary statements specific for combined pills were followed in a half. Most common adverse reactions were specified for most products, though short term disturbance of menstrual cycle were mentioned in less than a quarter. Few products mentioned health benefits other than contraception. Less than a half notified women of warning signs and symptoms of serious adverse effects of the pill. Package inserts of products under the same foreign manufacturers were similar in contents, and were lengthy compared with those of local products. Discrepancies and insufficiencies of the information provided in the package inserts existed among the oral contraceptive products marketed in Thailand. Users of a different brand of the products may thus benefit unequally. A specific guideline for producing a user-oriented package insert of oral contraceptive pill products is needed.

Key words

Oral contraceptives, Patient information leaflet, Patient package insert

Introduction

Drug Law and Regulation in Thailand requires that in order to register a drug product for marketing, manufacturers or importers of the drug product must submit a product labeling and a product leaflet or a package insert (1). The product container label must include; name of the product, its registration number, package size, generic name(s) as well as amount of active ingredient(s), production number, name of manufacturer, its location, date of production, classification of a drug according to law, and an expiry date. However, there is no specific requirement for presentation and format of a package insert. A proper font size was not specified, neither were reading skill or

grade level for intended users. These are in contrast to the practice in the European countries (2) and the US (3), where there are specific guidelines for developing a package insert, with the emphasis on its contents and readability. Foreign language label must be accompanied with its translated Thai version. For some products notified in Ministerial Regulations (1), precautionary words specific for each category of drug are compulsory at both the container label and the leaflet. Oral contraceptive pills are included.

In Thailand, oral contraceptive products are available via two channels, i.e., a community pharmacy and a family planning clinic at hospital or private clinic where a doctor or a nurse is a product provider and counselor. Community pharmacists are authorized to dispense an oral contraceptive product to clients after thorough history taking. Most women visit community pharmacy seeking and continuing their oral contraceptives. Pharmacists may consult textbook references as well as product leaflets or package inserts when advising and choosing a pill for clients. A few pharmaceutical companies manufacturing oral contraceptive pills published a mini booklet as a guide for users. However, it is not available to all community pharmacies. Users of oral contraceptives rely largely on pharmacists' verbal advices which are certainly not exhaustive. Referring to package inserts is, thus, indispensable. No research in Thailand has examined how and what drug information in oral contraceptive package inserts was presented and how community pharmacists and oral contraceptive users evaluated them. The objective of the present study was to examine and compare drug information presented in the package inserts of oral contraceptive pill products marketed in Thailand.

Materials and Methods

List of oral contraceptive pills registered for marketing in Thailand as of October 2004 was obtained from Drug Control Division under Food and Drug Administration (FDA). The products were purchased through community pharmacies. Their package inserts were retrieved and contents reviewed against each other. The contents were studied under the following headings:

1) How to start the first pack of pill
2) How to continue the following pack of pill
3) How to do when missing a pill or more
4) Contraindication for taking the pill
5) Precaution
6) Adverse Drug Reactions
7) Non-contraceptive benefits
8) When to see a doctor

In particular, the comparison of information on contraindication was referred to those categorized by World Health Organization (WHO) (4). The results were tabulated and frequencies were presented.

Results

1. Background information

There were 18 manufacturers of 94 registered brand name oral contraceptive pills in Thailand, as of October 12, 2004. One-third of the manufacturers were foreign pharmaceutical industries, while the rest were local companies. Twenty-four brand names of oral contraceptives from eight manufacturers were available for purchase from community pharmacies in a southern Thai province of Songkla, where the study took place. Table 1 shows the 24 brand names and their formulas. Over a half of the products were from four foreign pharmaceutical companies. All but one were combined pills, one of which was a triphasic formulation while the remaining were monophasic.

2. Comparison of contents provided in package inserts

2.1 How to start the first pack of pill (Table 2)

All 24 oral contraceptive products had clear instructions on how to begin the first pack. Three different methods for starting the pill were identified in the package inserts. Over a half (54%) advised taking the first pill on the first day of menstruation (method 1) as the only method. A

Table 1. Twenty four oral contraceptive products and their active ingredients

Brand names	**Estrogen component** (μg)	**Progestin component** (μg)	**No. of pills**
Anamai®	Mestranol (50)	Norethisterone (1000)	28
Anna®	Ethinyl estradiol (30)	Levonorgestrel (150)	28
Diane 35® Lady E 35® Preme® Sucee®	Ethinyl estradiol (35)	Cyproterone acetate (2000)	21
Exluton®	-	Lynestrenol (500)	28
JENY-FMP®	Ethinyl estradiol (50)	Norgestrel (500)	28
Gynera® Gynera ED®	Ethinyl estradiol (30)	Gestodene (75)	21 28
Margaret®	Ethinyl estradiol (50)	Ethynodiol diacetate (1000)	28
Marvelon®	Ethinyl estradiol (30)	Desogestrel (150)	21, 28
Mercilon®	Ethinyl estradiol (20)	Desogestrel (150)	21, 28
Meliane®	Ethinyl estradiol (20)	Gestodene (75)	21
Microgest ED®	Ethinyl estradiol (30)	Levonorgestrel (150)	28
Microgynon 30ED®	Ethinyl estradiol (30)	Levonorgestrel (150)	28
Minulet®	Ethinyl estradiol (30)	Gestodene (75)	21
Nordette®	Ethinyl estradiol (30)	Levonorgestrel (150)	21, 28
Noriday Brywood®	Mestranol (50)	Norethisterone (1000)	28
Ovral®	Ethinyl estradiol (50)	Norgestrel (500)	21, 28
Riget 21+7®	Ethinyl estradiol (30)	Levonorgestrel (150)	28
Rigevidon 21+7®	Ethinyl estradiol (30)	d-norgestrel (150)	28
Triquilar ED®	Ethinyl estradiol (30) Ethinyl estradiol (40) Ethinyl estradiol (30)	Levonorgestrel (50) Levonorgestrel (75) Levonorgestrel (125)	28
Yasmin®	Ethinyl estradiol (30)	Drospirenone (3000)	21, 28

quarter recommended beginning the first pill on day 5 of menses (method 2) as a single option. The least frequently cited method (method 3), i.e., taking the first pill during day 2 to day 5 of menstruation with a backup method was found in a further 12.5% which also offered the method 1. Around 8% provided users with method 1 and method 2. Only one product advised women with an irregular period or a shorter than 24 day menstrual cycle to begin the pill on the first day of menses.

2.2 How to continue the following pack of pill

All products had a clear instruction on how to continue the next pack of pill. Women may start a new pill pack right after finishing the last pill of the previous one, or after the 7-day pill free period, depending on if they were taking a 28-pill package or a 21-pill package, respectively.

2.3 How to do when missing a pill or more (Table 3)

One product did not give any particular advice at all. Among those, which did, advice on either missing one, two or three pills was presented. Twenty (83.3%) had a general instruction for missing one pill, with 66.7% were specific for

Table 2. Number of oral contraceptive package inserts with an instruction on how to start the first pack of oral contraceptive pills

How to start the pill	**No. of package inserts** (%) (N = 24)
Method 1 only Take the pill on the first day of menses	13 (54) [a]
Method 2 only Take the pill on day 5 of menses	6 (25)
Method 1 and Method 3 Take the pill during day 2 to day 5 of menses with a back up method for the first 7 days of taking the pills	3 (12.5)
Method 1 and Method 2	2 (8.3)

[a] One recommended the method for users having an irregular period or a shorter cycle than 24 days

Table 3. Number of oral contraceptive package inserts with an advice on how to do when missing a pill or more

What to do when missing a pill	**No. of package inserts** (%) [a] (N = 24)
None provided	1 (4.2)
Forgetting one pill	
- Take the missed pill as soon as remember	4 (16.7)
- Within 12 hours, take the missed pill as soon as remember	16 (66.7)
- Late more than 12 hours	
- Take 2 pills + back up method for 7 days	5 (20.8)
- Discard the missed pill, continue the pack + back up method	7 (29.2)
- Take the missed pill as soon as remember + back up method for 14 days or till finish pack	2 (8.4)
- Forgot during week 1, take the missed pill as soon as remember + back up method for 7 days	4 (16.7) [b]
- Forgot during week 2, take the missed pill as soon as remember	4 (16.7) [b]
- Forgot during week 3, take the missed pill as soon as remember, continue the pack, skip 7 day hormone free period and start a new pack	4 (16.7) [b]

Table 3. (continued)

What to do when missing a pill	**No. of package inserts** (%) [a] (N = 24)
Forgetting 2 pills	
- Take the missed pills as soon as remember + back up method for 14 days or till finish pack	2 (8.4)
- Discard the missed pills, continue the rest + back up method	7 (29.2)
Forgetting 3 pills	
- Discard the pack, start a new pack	1 (4.2) [c]
- Discard the missed pills, continue the rest + back up method	5 (20.8) [c]

[a] Sum of percentage exceeds 100 as some products provided more than one advice regarding the missed pills.
[b] They were the same products.
[c] They were among the nine products which had advice on forgetting 2 pills above.

missing the pill within 12 hours. Seventy-five percents (18/24) had a further instruction when being more than 12 hour late for one pill, where an additional back-up method was often recommended. Specifically, 16.7% detailed what to do if one single pill was forgotten in a particular week of the cycle. A recommendation when missing two or three pills was available in 37.5% (9/24) of the package inserts. Overall, a quarter (6/24) had in their package inserts the complete advice on what to do when missing one, two and three pills.

2.4 Contraindication for oral contraceptive use (Table 4)

Four clinical conditions frequently cited in the package inserts as being contraindicated to the pill use were current breast cancer (66.7%), benign hepatic neoplasia (62.5%), pregnancy (62.5%), and current deep vein thrombosis (58.3%). This corresponds with the category 4 of WHO eligibility criteria for contraceptive use (4), in which the pill is not to be used or considered contraindicated. The other less frequently presented contraindications which were compatible with WHO criteria of not using the pill (category 3 or 4) were postpartum breast feeding, diabetes with vascular complications, past deep vein thrombosis/pulmonary embolism, history of breast cancer, previous stroke, and malignant hepatic neoplasia. Conditions which were included in the package inserts as being contraindicated for the pill use, but were considered eligible for the pill use by WHO (category 1 or 2) were varicose veins (12.5%), benign breast diseases (4.2%), endometrial cancer (33.3%), sexually transmitted diseases and hepatitis (33.3%), family history of deep vein thrombosis or pulmonary embolism (12.5%), superficial thrombophlebitis (16.7%), undiagnosed vaginal bleeding (33.3%), and sickle cell anemia (29.2%). Sixteen product package inserts had a separate heading of contraindication for the pill use. In those which did not have, the clinical conditions appeared under precautionary topic. In addition, it was noted that products under the same manufacturer had very similar information and format.

2.5 Precaution

All products had in their package inserts a section of precaution, with 66.7% having both precaution and contraindication sections.

Table 4. Number of oral contraceptive package inserts presenting various contraindications to their use in reference to WHO eligibility criteria for contraceptive use

Clinical conditions contraindicated to pill use	**No. of package inserts** (%) (N = 24)	**WHO category**[a]	**WHO contraceptive eligibility**[b]
Varicose veins	3 (12.5)	1	The pill can be used
Breast tumours	1 (4.2)	1	
Endometrial cancer	8 (33.3)	1	
Sexually transmitted diseases including HIV infection and hepatitis	8 (33.3)	1	
Family history of deep vein thrombosis or pulmonary embolism	3 (12.5)	2	
Superficial thrombophlebitis	4 (16.7)	2	
Undiagnosed vaginal bleeding	8 (33.3)	2	
Sickle cell anemia	7 (29.2)	2	
Breast feeding (6 weeks to < 6 months post partum)	4 (16.7)	3	Do not use the pill
History of breast cancer without recurrence in past 5 years	7 (29.2)	3	
Diabetes with vascular complications	11 (45.8)	3	
Pregnancy or suspected	15 (62.5)	4	
History of deep vein thrombosis or pulmonary embolism	7 (29.2)	4	
Current deep vein thrombosis	14 (58.3)	4	Do not use the pill
History of stroke	4 (16.7)	4	
Current breast cancer	16 (66.7)	4	
Malignant hepatic neoplasia	9 (37.5)	4	
Benign hepatic neoplasia	15 (62.5)	4	

[a] WHO category
1: a condition for which there is no restriction for oral contraceptives use.
2: a condition where the advantages of using oral contraceptives generally outweighs the theoretical or proven risks.
3: a condition where the theoretical or proven risks usually outweighs the advantages of using oral contraceptives.
4: a condition which represents an unacceptable health risk if the contraceptive method is used.
[b] Where resources for clinical judgement are limited, such as in community-based services, the pill use is generally acceptable with no restriction for those falling to category 1 or 2. The pill use is contraindicated in those having conditions of category 3 or 4.

According to Thai Drug Law and Regulations, precaution must be provided for oral contraceptive products in general and specifically for post-coital pills as well as combined oral contraceptive pills (1). The general precaution for oral contraceptive products was as follows.

"Precaution:

1.Consult a doctor if you experience an unusual symptom

2.Contraindicated in occlusive vascular diseases, and hepatic diseases

And the specific precaution for combined oral contraceptives was;

"Precaution:

1.Consult a doctor if you experience an unusual symptom
2.Contraindicated in occlusive vascular diseases, leg varicose vein, and hepatic diseases
3. Should not be used in those at risk for occlusive vascular diseases, e.g. history of thrombophlebitis, thromboembolism, obesity, hypertension, and smoking"

Fifty-four percents of the combined pill package inserts had followed exactly the same specific statements aforementioned. Some (12.5%) expanded more on smoking, i.e. "cautioned in smoking women especially those from 35 years of age, a doctor should be consulted before using the pill". A further 33.3%, one of which was progestin-only pill, had provided only a general statement of the precaution as above.

2.6 Adverse drug reactions (Table 5)

Adverse effects related to the pill use were available in package inserts of 66.7% of the products. The information varied even among the products of the same type of hormonal ingredients. Breast effects (62.5%), headache (62.5%), depression (62.5%), gastrointestinal symptoms (58.3%), skin change (58.3%), intolerance to contact lens (54.2%), weight and appetite changes (54.2%) were the side effects most frequently informed. The followings were only cited in one or two brands; jaundice, increase in blood pressure, vaginal candidiasis, and varicose vein. The effect on menstruation, namely spotting and breakthrough bleeding, was mentioned in package inserts of only five products (20.8%). Of note, a serious rare adverse effect, i.e., thromboembolism was independently specified in package inserts of the products under foreign pharmaceutical companies, but not of the products under local companies.

2.7 Non-contraceptive benefits (Table 6)

One-third of the products included other benefits of taking oral contraceptive pills. Those containing cyproterone acetate (n = 4) or drospirenone (n =1) told users that the products would improve acne and oily skin/hair caused by androgen over-activity. These five package inserts did not mention any other benefits. Two products (8.3%) supported that the pill users would have less risk toward endometrial cancer, ovarian cancer/ cysts, pelvic inflammatory diseases, and ectopic pregnancy. Regular cycle control and reduced dysmenorrhea were also mentioned in the two brands (8.3%).

2.8 When to see a doctor

Less than a half (11/24) of package inserts told users when to stop taking the pills and see a doctor urgently. Most concern was related to thromboembolism which may have presenting symptoms as severe headache, migraine, sudden change in vision/speech/hearing, severe chest pain, dyspnoea, and severe abdominal pain.

It was also notable that the package inserts of oral contraceptive products from foreign pharmaceutical companies were lengthy in contents in comparison with those of local companies. Products under the same foreign companies have similar package inserts.

Discussion and Conclusion

Due to the lack of clear specific guideline on how and what a product package insert or leaflet should be presented, it was not surprising to see discrepancies among information contained in product leaflets of 24 different brand name oral contraceptive pills marketed in Thailand. Though the number of the products in the study represented only a quarter of total oral contraceptive products (24/94) registered for marketing in the country, it is anticipated that similar findings would be applied to the remaining products due to the absence of the specific guideline.

Overall, all products gave a clear instruction on how to commence and continue the pill. Most advised a single method when beginning the pill. The most common and effective method especially for the first cycle, i.e., taking the first pill on day one of menses (5, 6) was cited by about a half. However, women should be informed of an alternative choice in case the recommended method is not possible or not preferred. An alternative method allows women to begin the pill during day

Table 5. Adverse drug reactions informed in oral contraceptive package inserts

Adverse drug reactions	**No. of package inserts** (%) [a] (N = 24)
None provided	8 (33.3)
Breast tenderness	15 (62.5)
Depressive moods	15 (62.5)
Headache	15 (62.5)
Chloasma	14 (58.3)
Gastric upsets	14 (58.3)
Intolerance to contact lens	13 (54.2)
Weight & appetite changes	13 (54.2)
Change in libido	12 (50.0)
Fluid retention	7 (29.2)
Spotting and breakthrough bleeding	5 (20.8)
Change in vaginal discharge	4 (16.7)
Vaginal candidiasis	2 (8.3)
Jaundice	1 (4.2)
Varicose vein	1 (4.2)
Increased blood pressure	1 (4.2)
Others (alopecia, insomnia, fatigue)	1 (4.2)

[a] Sum of percentage exceeds 100 as each product cited more than one adverse drug reaction.

Table 6. Non-contraceptive benefits presented in oral contraceptive package inserts

Non-contraceptive benefits	**No. of package inserts** (%) [a] (N = 24)
None provided	16 (66.7)
Anti-androgenicity effects (acne, oily skin/hair, hirsutism)	5 (20.8)
Cycle regularity and improved dysmenorrhea	3 (12.5)
Reduced risk of breast cancer	1 (4.2)
Reduced risk of the following; - ovarian cancer - endometrial cancer - ovarian cyst - pelvic inflammatory diseases - ectopic pregnancy	2 (8.3) [b, c]

[a] Sum of percentage exceeds 100 as some products cited more than one benefit.
[b] They also mentioned benefit toward the cycle control and dysmenorrhea.
[c] One of these also mentioned reduced risk of breast cancer.

2 to day 5 of menstruation where a back up method should be used for an extra precaution for a starter. It was offered in only few products (12.5%). Furthermore, the study found less than a quarter of the package inserts provided two choices for beginning the pill. The results indicated pill clients may not be able to depend on the advice in the pill package insert. Moreover, these highlighted the importance of pharmacist's verbal communication with clients the flexibility in starting the pill while retaining its effectiveness.

One of the most important advices is how to do when missing a pill as this may be associated with contraceptive failure if users are not aware of the solution and do not act promptly enough. Though majority had the instructions when missing one single pill, more than a half had no instruction on how to act when missing two or more pills. Furthermore, a combination of both advices was found in only a quarter of the package inserts. The present study found the essential information was inadequate. This may be of concern as it is not possible for a community pharmacist to verbally discuss at one encounter all the pill rules. More details should thus be available in the package insert for users to refer to when necessary in order to act in a timely manner regarding missing pills. A study in almost 1000 women showed that during the first few months after initiating the pill nearly half of the women missed one or more pills in a cycle, while almost a quarter reported missing two or more pills (7). Risk of missing more pills was found in those not reading or not understanding the pill package insert.

According to the recommendation from WHO (4), there were clinical conditions in which oral contraceptive pills can be used, and those in which the pills are not to be used. The recommendation is intended for the use in primary care service where thorough physical examination/investigation apart from careful history taking is not practical. It also applies to the practice in community pharmacy in Thailand. The present study found information on contraindications was available in two-thirds of the package inserts. However, they did not distinguish between conditions where benefits outweighing risks from taking the pill, thus some disorders were listed as being contraindicated to the pill use, as opposed to those recommended by WHO. A study of 20 oral contraceptive pill packages in Italy (8) found even more broad contraindications such as pruritis, thromboplebitis, hypertension, diabetes, lipid disorders, cardiovascular diseases, cerebro-vascular diseases, and unspecified neoplasia. Based on the package inserts, a pharmacist or a doctor may be reluctant to recommend the pill to clients. This might deprive women of available choices in contraception as well as benefits from using the pill. However, there is no study of factors related to women's medical histories or current medical conditions that would affect prescribing or dispensing oral contraceptives.

All 24 oral contraceptive products contained a precaution heading in their package inserts, in compliance to Drug Law and Regulation specific to oral contraceptive products previously mentioned. General precaution for oral contraceptive pills and specific precaution for combined pills were required (1). The specific statements for the combined pills were followed in only a half of the products. A third provided only a general precaution. Therefore, the regulation was not completely followed. A general statement warns users to consult a doctor if experiencing unusual symptoms. This was clearly not specific, but was present in all products' precaution. It was later elucidated in a separated heading of 'when to see a doctor' as alarming signs and symptoms such as severe headache, sudden change in vision/ hearing/ speaking, sharp pain in the chest, dyspnea, breast mass, and jaundice. Such warnings were not available for users in over a half of the package inserts. The Drug Law and Regulation further requires precautionary statements of clinical conditions in which the use of oral contraceptives are contraindicated or not recommended. They were mostly involved with vascular occlusive diseases and hepatic diseases. The information were redundant to those provided in the contraindication section of the package inserts.

Adverse drug reactions related to the use of oral contraceptives were not available in one-third of the product package inserts. An effect on menstruation, i.e., spotting and breakthrough

bleeding, which occurs frequently during the first few months of use was mentioned in only one-fifth of those having adverse drug effects information. This was of concern as it was the main reason women discontinued their pills (9). Thus, rather than relying on written information, pharmacists must assure new users verbally that those are not harmful to health and will subside with continuing use. Most common adverse effects frequently cited were breast tenderness, depressive moods, headache, chloasma, and gastric upsets. The result was similar to that of the Italian study (8). Weight gain remained included as a side effect in almost all package inserts though with insufficient evidence to support its causal relation to combined oral contraceptives (10).

Apart from contraceptive purpose, oral contraceptive pills provide both cycle and non-cycle benefits in a long term which might improve adherence to pill use. However, a few oral contraceptive products provided the information. In fact, some particular products with a hormonal ingredient possessing a distinguished property, such as those containing antiandrogenic cyproterone acetate, was not indicated primarily for contraception but androgenization condition in women. The finding again was in accordance with what found in the other study (8).

In addition, it was found that letter size of most package inserts was so small that readability might be a problem in some users. Though the Drug Law and Regulation requires that they should be clearly readable, the size of letter was not specified. Besides, length of the leaflet, reading level, wording, lay language and medical terminology used were apparently left to the manufacturers to decide. A further study may obtain users' evaluation of the usefulness and readability of oral contraceptive package inserts. Some studies showed that consumer oriented- or user testing of package insert or patient information leaflet was the effective method in producing comprehensible patient package insert (2, 11, 12). Thus, users of different oral contraceptive pill products in Thailand may not be equally informed of drug information in the product package inserts due to the discrepancies in the provision of drug information. They therefore would benefit differently. The lack of specific guideline in producing patient information leaflet or product package insert for oral contraceptive pills may be an explanation for the discrepancies. Consistency in contents, readability and font size must also be considered. Developing the leaflet should be user-oriented, thus research is further needed in Thailand on user evaluation of the package insert. However, provision of the leaflet does not preclude verbal discussion between a client and a provider. A randomized controlled trial showed that both offered together largely improved knowledge of contraception in women already taking the pill (13). Issues pertaining to oral contraceptive effectiveness and extra benefits to health should be made available. Users should also be aware of flexibility in starting the pill while retaining its effectiveness in contraception, as well as of specific advice on what to do if missing a pill or more and when they should seek an emergency contraception. The study found insufficiency and discrepancies of essential information in the oral contraceptive pill package inserts. Drug Control Division, Food and Drug Administration may have to revise the present guidance for oral contraceptive patient package insert.

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