1st SCIENTIFIC SYMPOSIUM OF THE ASIA-PACIFIC COUNCIL ON CONTRACEPTION

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Shanghai, China

THEME

Towards Safe, Effective and Acceptable Contraception For All

ASIA PACIFIC COUNCIL ON CONTRACEPTION.

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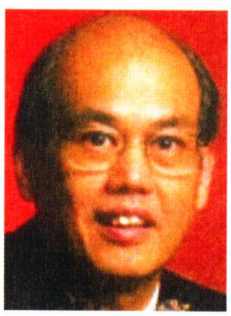

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Welcome to the Asia Pacific Council on Contraception (APCOC)!

Across the Asia-Pacific region, there exist wide variations in the acceptance of modern contraceptives. Low acceptance rates of oral contraceptives, for example, generally correlate with a high incidence of abortions and unwanted pregnancies.

Notwithstanding the thousands of deaths arising from unsafe abortions every year, this situation also places a tremendous health, social, psychological and economic burden on the female population of these countries, who are often the most vulnerable members of their societies. In order to improve their situation, the expertise and resources of all stakeholder groups associated with family planning are required, as well as collaboration between these stakeholder groups.

APCOC develops education and awareness programs targeting healthcare professionals associated with contraception and family planning. As a body representing all of Asia and Pacific, APCOC also takes the responsibility to co-ordinate these programs from a pan-Asian perspective.

APCOC unites leading specialists in obstetrics and gynecology who are interested in contraception and family planning medicine and dedicated to improve women's health across the region. The objective of this council is to **advance knowledge and create awareness** regarding contraception and family planning medicine among healthcare providers, governments, and the general public. By doing this, APCOC will directly improve the health and well-being of millions of women and children.

The primary method to achieve these objectives will be to **exchange best practices regarding contraception and family planning education** with an aim to increasing female health care and well being. To succeed, APCOC must **create and maintain relationships** with medical societies, governments, non-governmental organizations, contraception providers and end-users. APCOC will not only improve medical practice but also play an important role in educating women all across the Asia Pacific region in both the private and public healthcare sectors.

Mission Statement

The Asia Pacific Council on Contraception (APCOC) was founded in 2006 by leading regional experts in the field of contraception and family planning.

APCOC's main goals are to:

- Highlight the importance of family planning, with safe and reliable contraception across Asia Pacific.
- Empower women in Asia Pacific with reliable information, education and communication to provide them with the opportunity to make informed choices in contraception.
- Tackle contraception related issues and provide contraception education for the general public, in particular women in Asia Pacific, and disseminate best practice strategies for healthcare providers.

APCOC's primary mission is to create effective family planning and contraception programs and educational materials by collating the best practices and extensive expertise of its members. APCOC strives to be instrumental in improving women's health across the region through educational programs, medical meetings/ congresses, publications, the media, and other relevant communication channels.

In addition, APCOC seeks to influence the development of reproductive healthcare policies in the Asia-Pacific region, by advocating approaches to contraception that are appropriate to individual countries' respective healthcare systems, social and cultural values, and economic frameworks.

Because APCOC represents the leading experts in Asia-Pacific, it is ideally placed to implement these best practices and state-of-the-art educational programs, activities and materials in the clinical practice of all countries in the region through outreach to medical societies, governments, non-governmental organizations, teachers and the general public.

Scope and Objectives

APCOC is committed to raising awareness and conducting programs in:

- Contraception
- Family planning/spacing
- Abortion & teenage pregnancy
- Sexually transmitted diseases

APCOC's distinguished and esteemed faculty are recognized throughout the Asia-Pacific region as authoritative expert sources of information and knowledge in contraception and family planning.

APCOC advocates the best global practices in awareness creation and program implementation, and promotes these best practices locally through:

- Language and culture-specific education initiatives targeting health care professionals, teachers and the general public
- Advocacy activities to influence healthcare policy and practice on a macro level
- Collaborative partnerships with other NGOs to raise awareness of issues related to contraception and family planning

Your Life, Your Family, Your Freedom

The theme *'Your Life, Your Family, Your Freedom'* encapsulates APCOC's aim of empowering women with reliable "Information, Education and Communication" to make informed choices on health, contraception and family planning.
Separately, each element of the theme relates to APCOC's mission.

- **Your Life** relates to women's lives. A woman who makes informed health and childbearing decisions is in control of her life.

- **Your Family** refers to a woman's immediate family. A woman's decisions in health and childbearing will have a direct impact on the health and well-being of her husband and children. By making informed childbearing decisions, a woman can improve the health and well-being of her family.

- **Your Freedom** encompasses a woman's life and family. APCOC aspires to give women the freedoms they desire in life – the freedom to fulfil life dreams and to give their best to the family – by empowering them with reliable "Information, Education and Communication" to make informed choices on health, contraception and family planning.

THURSDAY, NOVEMBER 8, 2007

0800-0950 **Arrival & Registration**

0950-1000 **Opening Remarks**
Prof Soo-Keat Khoo (Australia)

1000-1100 **Plenary 1**
Chairpersons: *Prof Biran Affandi (Indonesia)*
Prof Linan Cheng (China)

Effective Contraception Saves Life
Prof Raquel D. Arias (USA)

1100-1215 **Symposium 1**

Adolescent and Contraception
Chairpersons: Dr Dominic Fuk-Him Li (Hong Kong)
Prof Im-Soon Lee (Korea)

1.1 Problems in Adolescents
Prof Grace Tang (Hong Kong)

1.2 Hormonal Methods for Emergency Contraception
Prof Linan Cheng (China)

1.3 Contraceptive Behaviour of Adolescents in China
Dr Xu Jieshuang (China)

1215-1330 **Lunch**

1330-1430 **APCOC Initiatives**

Chairperson: Prof Soo-Keat Khoo (Australia)

1. Evidence Based Consensus in Contraception
   Prof Ma. Antonia E. Habana (Philippines)
2. Continuing Medical Education in Contraception
   Assoc Prof P. C. Wong (Singapore)
3. Sex Education
   Prof Surasak Taneepanichskul (Thailand)

1430-1530 **Symposium 2**

Safety Issues on Contraception

Chairpersons: Prof Jamiyah Hassan (Malaysia)
Prof Biran Affandi (Indonesia)

2.1 Results of a Large Active Surveillance Program in Europe
Dr Maureen Cronin (Germany)

2.2 Specific Issues Associated with Contraception
Prof Lee P. Shulman (USA)

2.3 Long-term Safety of Contraception
Prof Li Ying (China)

1530-1600 **Tea**

1600-1700 **Plenary 2**

Chairpersons: Prof Soo-Keat Khoo (Australia)
Assoc Prof Cherng-Jye Jeng (Taiwan)

Cancer Phobia and Hormonal Contraception
Prof Ronald T Burkman (USA)

1700 **Closing Remarks**
Prof Soo-Keat Khoo (Australia)

Effective Contraception Saves Life
Professor Raquel D. Arias

More than one third of pregnancies in developing countries are unintended and most of these unintended pregnancies occur among women using no contraception. This leaves tremendous opportunity to reduce unsafe pregnancy terminations, spontaneous abortions, ectopic pregnancies, birth-related injuries and provide for greater investment in each child. The goal of assisting women and men in the achievement of their desired family size remains unmet in much of the world. Sadly, even the developed world has examples of unmet need. In the United States about half of pregnancies are unplanned. The barriers to effective use vary by region, as well as by the woman's education, degree of poverty, and marital status. Generally speaking, poor women in rural areas are at the greatest risk of unplanned pregnancy.

Women in committed relationships who do not use contraception are more likely to say it is because of a lack of access to supplies and medical services. They also cite concerns regarding side effects (perceived as well as actual), health effects (including future fertility) and inconvenience. These method-related effects are also among the most often cited reasons for method discontinuation. Misperceptions regarding personal risk of pregnancy are also common among non-users of contraception.

Most women at risk for unintended pregnancy are open to the concept of contraception and state that they will use it in the future. The most acceptable form of contraception may vary but accessibility, ease of use, and convenience of the method are all important. The provision of accurate and understandable information regarding effectiveness, side effects, and noncontraceptive benefits would do much to improve family life for the more than 100 million women with an unmet need for contraception.

Problems in Adolescents

Professor Grace Tang

Adolescent reproductive health has been an area of concern and study since the 1994 international conference on population and development in Cairo where governments were urged to improve the sexual and reproductive health of adolescents through provision of integrated health services including contraception and health education. The intention is to provide adolescents knowledge about sexual relationship and its consequences such as unwanted pregnancy leading to its termination, sexually transmitted diseases, premature parenthood, and effects on their future. There should also be provisions for safe sexual activity such as contraception should it be needed. There is no denial that sexual activity in adolescents is not uncommon.

Generally, the use of contraception in adolescents is inconsistent, and the behavior is not only related to the availability of methods, but also to the environment, the culture, the parents, the communication, and the attitude of adolescents themselves.

The most widely used methods are the condom and the contraceptive pills, but the duration of use is often variable and not lasting. Condom may have an advantage over other methods in its non-invasiveness, lack of side effects and most importantly, its ability to protect against sexually transmitted diseases.

Adolescent pregnancies pose problem to the youths, their family and the Society. There are fluctuations in the rates of pregnancy and abortion. There appears to be some decline in the rates in some places, but the reasons for such decline are not apparent.

There is need for continued effort to assist adolescents in their sexual and reproductive health. Physicians must be proactive in rendering such services by providing appropriate sexual health information and services when they provide other clinical services to youth. They must be ready to enquire. They must be well versed in the subject of adolescent sexual and reproductive health-care.

Hormonal Methods for Emergency Contraception

Professor Linan Cheng
Shanghai Institute of Family Planning Technical Instruction
The International Peace Maternity & Child Health Hospital, Jiao Tong Medical College. (email: linanc@online.sh.cn)

Background: Emergency contraception is using a drug or copper intrauterine device (Cu-IUD) to prevent pregnancy shortly after unprotected intercourse. Several interventions are available for emergency contraception. Information on the comparative efficacy, safety and convenience of these methods is crucial for reproductive health care providers and the women they serve.

Objectives: To determine which emergency contraceptive method following unprotected intercourse is the most effective, safe and convenient to prevent pregnancy.

Main results: Eighty-one trials with 44,103 women were included. Most trials were conducted in China (71/81). There were more pregnancies with levonorgestrel compared to mid-dose (25-50 mg) (15 trials, RR: 2.01; 95% CI: 1.27 to 3.17) or low-dose mifepristone (<25 mg) (9 trials, RR: 1.43; 95% CI: 1.02 to 2.01). Low-dose mifepristone was less effective than mid-dose (20 trials, RR: 0.67; 95% CI: 0.49 to 0.92), but this effect was no longer statistically significant when only high quality trials were considered (6 trials, RR: 0.75; 95% CI: 0.50 to 1.10). Single dose levonorgestrel (1.5 mg) administration seemed to have similar effectiveness as the standard 12 hours apart split-dose (0.75 mg twice) (2 trials, 3830 women; RR: 0.77, 95% CI: 0.45 to 1.30). Levonorgestrel was more effective than the Yuzpe regimen in preventing pregnancy (2 trials, RR: 0.51; 95% CI: 0.31 to 0.83). CDB-2914 (a second-generation progesterone receptor modulator) may be as effective as levonorgestrel (1 trial, 1549 women; RR: 1.89; 95% CI: 0.75 to 4.64) but the confidence interval is wide and the result compatible with higher or lower effectiveness. Delay in the onset of subsequent menses was the main unwanted effect of mifepristone and seemed to be dose-related.

Conclusions: Mifepristone middle dose (25-50 mg) was superior to other hormonal regimens. Mifepristone low dose (<25 mg) could be more effective than levonorgestrel 0.75 mg (two doses) but this was not conclusive. Levonorgestrel proved more effective than the Yuzpe regimen. The copper IUD was another effective emergency contraceptive that can provide ongoing contraception.

Contraceptive Behaviour of Adolescents in China

Dr Xu Jieshuang

Along with the open policy since the end of 1970s, attitudes and values towards premarital sexual behavior had been changed dramatically in China, which would inevitably affect adolescent population. Boys and girls nowadays have experienced puberty at younger age than previous generation. The percentage of sexually active adolescent is different at different population between 2.2%-11.3%, but male is higher than female. Very high percentage of them doesn't use any protection at the 1st intercourse; consistent use of contraception is even lower. Girls seldom use oral contraception because misconceptions are very common among them and peers. The most widely used contraception in turn is condom, withdrawal and fertility awareness. Because of lack of reliable contraception, some girls rely on Emergency Contraception even though they don't have sufficient knowledge of how to use, which leads to higher user failure rate of EC. Qualitative researches show that not only poor knowledge, attitudes and perception about contraception including condom leads to lower contraception use, but also other reasons such as poor access to FP services, alcohol use, sexual coercion, less negation power among girls, RTIs/STIs, even HIV/AIDS. Adolescents in China are facing a series of reproductive health problems, unintended pregnancy, unsafe abortion, abortion and delayed abortion. Studies focusing on adolescent population are still very few in China. We suggest that related data should be integrated into national survey. Further gender related issue researches and qualitative data are required to explore in-depth information for future interventions and policy development.

The Use of Evidence Based Medicine in Promoting the Social Acceptance of Family Planning in the Philippines

Professor Ma. Antonia E. Habana

Background:

Family Planning is one of the programs of the Philippine Department of Health, yet a lack of new information and some misinformation pose as barriers to popular acceptance and use of modern methods.

Objective:

To provide new and correct information about modern methods of family planning using EBM techniques.

Main outcome measures:

A series of Critically Appraised Topics (CATs) on selected Family Planning issues common in the Philippines was prepared by physicians trained in EBM.

Results:

Two training programs on EBM (Research Question Formulation, Searching the Medical Literature, Critical Appraisal, CAT Writing) were conducted with 60 participants. Several topics on the common perceived effects of hormonal contraceptives, surgical sterilization, modern natural family planning, intra-uterine contraceptive device and barrier methods were studied. The best article following the hierarchy of evidence was chosen as the basis for the prepared CAT. In a period of two and a half years, about 40 CATs have been prepared, published, and distributed. In the information kit was an introduction to EBM, especially prepared for the large number of potential users who are not familiar with the method. A laversion of each of the CATs was also prepared for the general public.

Conclusion:

EBM was used as the strategy to provide critical updates and to correct misconceptions about contraceptive methods. The evidence based material was to be used in the advocacy, information and education for Family Planning use. These CATs on FP were also used as material for manuals and clinical practice guidelines. The use of EBM by these trained individuals to prepare CATs was to ensure that the knowledge and skills to answer clinical questions on FP (and other reproductive health issues) would be used in a sustained manner.

Continuing Medical Education in Contraception

Associate Prof PC Wong
Department of Obstetrics and Gynaecology
National University of Singapore
National University Hospital

The Asia-Pacific Council on Contraception was established in 2006 with the objectives:

a) to advance knowledge and create awareness regarding contraception and family planning medicine among healthcare providers, governments, and the general public.

b) to provide knowledge and expertise to combine the best practices of all participating members in creating the most effective family planning and contraception programmes, activities, and educational materials.

c) to shape a strategy towards contraception that is cognizant of healthcare systems, social frameworks and economic values and the basic necessity for contraception with a view to influencing reproductive healthcare policy within the Asia Pacific region.

One of the four projects that have been identified by the Council is to develop a special CME (Continuing Medical Education) Module for Obstetricians & Gynaecologists, General Practitioners and Family Planning Staff and Midwives in contraception. We felt that our Health Care Providers (HCP) need to be updated with the best practice approach and modern practice of contraception and family planning.

The Module consists of 14 Chapters covering all the aspects about various methods of contraception. It also has a section on commonly asked questions with case reports etc.

Understanding that in various countries, HCP are different, this Module comes in 3 versions - for the Obstetricians & Gynaecologists, GPs, and Midwives. The prototypes are being tested in Singapore, Indonesia and China. Once the field tests are completed satisfactorily, it can be rolled out to all countries in Asia-Pacific.

A Development of Sexual and Reproductive Health Services for Thai Adolescents

Professor Surasak Taneepanichskul, MD, M.Med (PH), LL.B, FRTCOG, FRTCPM
Dean, College of Public Health Science
Chulalongkorn University, Bangkok, Thailand

Introduction:

Thai societies are currently going through rapid change due in part to new information technologies and the process of globalization. These changes are shifting traditional behaviours particularly in the area of sexuality. These processes have influenced norms and behaviours among Thai adolescents who are increasingly engaging in risky sexual behaviours leading to declining health and well-being.

Adolescence is a time of tremendous opportunity and change. There are many factors that contribute to this vulnerability such as, rapid social change, earlier start to puberty, the impact of mass media, contacts across cultural boundaries and consumerism – globalization. The resulting problems are numerous; premarital sex, unsafe sex, teenage pregnancies, unintended pregnancy, abortion, sexual abuse and violence, STIs, and HIV/AIDS.

In order to deal with the multitude of problems that today's adolescents are facing, programs must be multidisciplinary, holistic and users friendly. With the philosophy of "Sexual Literacy" in mind, the Institute of Health Research (IHR), Chulalongkorn University has already developed a few sexual health programme. Some of them had been carried out successfully to date.

Objectives:

The overall aim of the programme is to:

1. Promote and operate adolescent reproductive health counseling courses for teachers.
2. Develop comprehensive model on providing human sexuality education to adolescents and provide reproductive health and related services for adolescents that are youth friendly and responsive to their needs.

Methodology:

IHR and the Department of Health (DOH), under the Ministry of Public Health (MOPH) in collaboration with Bansomdejchaopraya Rajabhat University introduced this program to promote reproductive and sexual health among Thai adolescents. The IHR had the detailed activities as follows:

1. **School Curriculum**
   - Development and Standardization of Teaching Packages for teaching of students
   - Training Workshop for Counselling in Human Sexuality Problems for selected teachers from 11 schools (10-day)
   - Teachers Training Course in Practical Use of Teaching Packages (5-day)
   - Actual Teaching Practice for teachers in classrooms with the supervision of Tutors
   - Allied-teachers Training Workshop

2. **Peer Helpers Training Course (3-day camp-training)**

3. **Youth Centre**
   - After-school and week-end Activities

Sexuality Educators Training:

Year 2004

The IHR organized two training courses entitled "Training Workshops for Counselling in Human Sexuality Problems" on 3rd – 14th May 2004 and the "Teachers Training Course in Practical Use of Learning Packages" on 17th – 21st May 2004. Twenty teachers from eleven secondary schools attended these training courses.

Year 2005

Disseminating of Sexual Education and Teaching Packages to new schools in Bangkok and provinces.

Four training courses entitled "Training Workshops for Counselling in Human Sexuality Problems" were organized on 21st March – 1st April and 10th – 21st October 2005 and the "Teachers Training Course in Practical Use of Learning Packages" on 9th-13th May 2005 and 11th – 20th October 2005. Forty teachers from twenty secondary schools attended these training courses.

Teaching Packages:

The Teaching Packages were modified and provided to 20 participating schools:-

- Transparencies 16 Chapters (approx. 200 illustrations per set/per school)
- CD-ROMs with a manual
- Sexuality Handbook
- Anatomy Posters (male and female)

Discussions and Recommendations:

IHR developed and standardized the Sexual Education Module including the Teaching Packages/CD ROMs and manuals. This Module was implemented in 11 schools in 2004 and 20 schools in 2005 for students of grades 10-12.

Most schools have been doing satisfactorily. In particular, the Catholic schools have performed remarkably well and on their own initiative adapted and extended the curriculum to lower graders and shared their experience with other Catholic schools outside our network. Therefore, in 2006 the Director of Education Department of Archdioceses agrees to expand the Sexual Education to other 40 Catholic Schools Bangkok Archdioceses, and also expand to all Catholic Schools in Thailand in near future.

Results of a Large Active Surveillance Program in Europe

Dr Maureen Cronin

Methods, study performance, and baseline risk

The European Active Surveillance (EURAS) Study was a prospective, controlled, non-interventional, active surveillance cohort study which was primarily designed to characterize and compare the risks of short- and long-term use of oral contraceptives (OCs). The primary outcome of interest was cardiovascular outcomes, in particular the incidence of venous thromboembolic events (VTE) but also arterial thromboembolic events (ATE) and arrhythmia, during OC use with particular focus on a newly marketed OC (Yasmin) containing a novel progestogen (DRSP).

A total of 59,510 OC users were enrolled by 1,113 study centers in 7 European countries. A total of 58,674 study participants were followed up for 142,475 women-years of observation. Overall, 1,401 women, or 2.39%, were lost to follow-up. The large size of the study and the very low loss to follow-up qualify the study to be a valid instrument to investigate rare serious adverse events (SAE) in a population of young, healthy women.

Three OC user cohorts were followed throughout the study. The cohorts were defined by the progestogen component in the OC that the woman took during the study: DRSP cohort, LNG cohort, and Other OC cohort. Overall, baseline risks were comparable between the cohorts, with the exception that the DRSP cohort demonstrated a slightly higher cardiovascular risk at study entry (i.e.; more women who were overweight/obese and/or had elevated cholesterol). This, however, did not have a major effect on the overall study results.

Three analyses were conducted with the final study data (as treated: AT; intention to treat: ITT; and per protocol: PP). Major differences were not found for these different analyses. Also separate analyses were conducted for OC starters and OC switchers without demonstrated differences. Given the fact that this was a drug safety study, the a priori defined primary analysis was the AT analysis for the three OC cohorts.

Follow-up results

The clinical outcomes were validated according to pre-defined algorithms and the VTE results were verified in a blinded adjudication process. The overall rates of any adverse events (AE) were similar for all cohorts (~1,300 AE/104WY). Also, the overall SAE rates were very similar for all three OC cohorts (~340 SAE/104WY). Major differences between the users cohorts were not found in the reporting pattern of AEs/SAEs nor in the organ system affected.

For the main outcomes of interest, cardiovascular events, which include reports on VTE, ATE and arrhythmia, major differences in the risk estimates between cohorts were not found. Based on Cox regression analysis, using the pre-defined confounder variables (i.e.; for VTE: age, BMI, duration of use, and VTE history; for ATE: age, BMI, smoking, and hypertension, for arrhythmia: age and BMI), no increase in risk was found for Yasmin users compared to LNG and Other OC users or for the combination of both of these cohorts (see table below).

	Yasmin vs. LNG		**Other OCs**		**LNG & Other OCs**	
	HR	95% CI	HR	95% CI	HR	95% CI
VTE	1.05	0.61-1.81	0.77	0.48-1.26	0.87	0.55-1.37
ATE	0.25	0.05-1.17	0.34	0.08-1.52	0.30	0.07-1.29
TE*	0.85	0.51-1.42	0.69	0.44-1.12	0.76	0.49-1.17
Arrhythmia**	0.52	0.22-1.22	0.77	0.34-1.76	0.65	0.30-1.40

* **all thromboembolic events (VTE and ATE combined)**
** **new conditions that required treatment**

The low ATE hazard ratios for the Yasmin cohort - in comparison to the two other OC cohorts - is noted. However, a statistically significant advantage for Yasmin was not demonstrated in this study.

Overall, all VTE, ATE and TE hazard ratios (adjusted and crude) that compared the DRSP cohort with other OC cohorts are close to or lower than unity and do not suggest a higher risk for Yasmin users. The narrow confidence intervals suggest that the risks for the three cohorts are similar.

Conclusions

No major differences were found between the cohorts in the rates for overall AEs and SAEs, organ-system specific SAEs, overall mortality and outcome-specific mortality, overall cancer and organ-system specific cancer, renal and hepatic dysfunction, unwanted pregnancy, and congenital malformations.

Overall, for all outcomes studied an increased risk in Yasmin users compared to users of other OCs (including LNG-containing OCs) was not identified. The study results were robust enough to show non-inferiority of Yasmin regarding the cardiovascular outcomes of interest. These results suggest that the risk of adverse cardiovascular outcomes for Yasmin use does not differ materially from the risks associated with the use of LNG-containing OCs or Other OCs.

Specific Issues Associated with Contraception

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The worldwide use of contraception is associated with an overall profound reduction in morbidity and mortality, primarily from the prevention of unintended pregnancy that is associated with a wide spectrum of lifestyle and life-threatening problems. Despite the wide recognition of this beneficial effect, many women and clinicians worldwide express concerns about the safety of contraceptive methods, including hormonal and non-hormonal methods. Although the use of any drug or device is associated with the potential for adverse events, including life-threatening events, it is well established that reversible contraception is associated with a considerably beneficial risk profile. Nonetheless, recent publicity of anecdotal events ostensibly associated with the use of particular contraceptives has furthered the concerns of some regarding the use of certain contraceptives. This presentation will provide current information concerning the safety of conventional and newer contraceptive methods and show that available contraceptives provide safe and reliable pregnancy prevention.

Long-Term Safety of Low-Dose COC Used in Chinese Women

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Abstract

Combined oral contraceptives (COC) have been popular for their effectiveness, convenience and reversibility since 1960s. There has however been increasing awareness of the risk of cardiovascular diseases (stroke, myocardial infarction and venous thromboembolism). Recent research has shown that there was an association between COC exposure and stroke in women. The pathogenesis of stroke is extremely complicated, and is determined and affected by multiple factors.

Purpose:

To clarify the long-term safety of use of widely distributed low-dose combined oral contraceptives (COCs) in China to decrease adverse reactions to COCs.

Methods:

A prospective surveillance cohort study was undertaken in 25 towns in two counties in Jiangsu Province, China. 44,408 women on hormonal contraceptives (HC) and 75,230 women with an intrauterine device (IUD)
were followed up from July 1997 to June

2000 to study the difference in the incidence of stroke. The case-control study based on the population of 25 towns in surveillance regions from July 1, 2000 to June 30, 2004, the stroke index cases (15 7) were living and married women who were born after June 1932 and had stroke for the first time. Married hospitalized women with other diseases or neighborhood but cardiovascular diseases were selected as controls (267) at the same period as cases with age no more or less than 3 years compared with the cases.

Results:

1. The incidence of haemorrhagic stroke (age-and-county standardized rate) was far higher than that of ischaemic stroke (34.74 vs 11.25 per 100,000 person years) among HC cohort.

2. The relative risk (RR) of incidence of haemorrhagic stroke in the HC cohort (52 cases) was 2.72 times compared with that in the IUD cohort (23 cases).

3. In women aged less than 45 years, compared to IUD users , the haemorrhagic stroke was strongly associated with current use of low-dose combined norethisterone pills, with RR being 19.06 (95%CI: 3.08-118.03).

4. Compared with IUD users, the current users of HC had a higher RR of 4.20 (95%CI: 2.11-8.36) of haemorrhagic stroke, and still reached 2.17 (95%CI:1.16-4.06) among past users after they had stopped taking COC for more than 10 years.

5. The RR of haemorrhagic stroke was 3.09 (95%CI: 1.26-7.57) among women who had last used low-dose COC during the previous five years.

6. The mean systolic blood pressure (MSBP 162.48±26.21 mmHg) of stroke group was significantly higher than that of control subjects by 33 mmHg ($P<0.01$), and the mean diastolic blood pressure (MDBP 95.28±15.05mmHg) of stroke group was significantly higher than that of control subjects by 16 mmHg ($P<0.01$).

7. Serum levels of TC, TG, APOB and Lpa of the cases were significantly higher than those of the controls, but the level of HDL-C of the cases was significantly lower than that of the controls. For hemorrhagic stroke cases, the levels of TC and APOB were lower than those of the controls, while for ischaemic stroke cases, the levels of TC, TG, APOB and Lpa were all lower than those of the controls.

8. Joint effects of risk factors on stroke
   After adjustment for age and residential region, stratified analyses showed evidence of joint effects of risk factors on risk of stroke as follows:
   Joint effect of history of hypertension with exposure of COCs (risk for all stroke OR=23.58, 95%CI 9.50-58.45, for hemorrhagic stroke OR=28.66, 95%CI 7.93-103.61 and for ischemic stroke OR=18.04, 95%CI 5.45-59.69).
   Joint effect of hyperlipemia and exposure of COCs (OR=4.72, 95%CI 2.39-9.29).
   Joint effect of hyperlipemia with history of hypertension (OR=18.60, 95%CI 8.09-42.78).

Conclusions:

1. There is certain association between increased risk of hemorrhagic stroke and use of the low-dose COC containing Norethisterone, appears to persist long after discontinuation, but effect may be reversible in prospective cohort study.

2. It is clear that hypertension, hyperlipemia and COC use were significant risk factors for stroke, and that the joint effects of COC exposure and both hypertension and hyperlipemia significantly increased the risk of all stroke in case-control study.

Suggestions:

1. Consider withdraw some COCs with serious adverse reactions.

2. Re-evaluate contraceptives, re-formulating quality criteria.

3. A post-marketing surveillance system for contraceptive drugs and devices should be established.

4. Improvement of blood pressure screening and follow up monitoring among population of hormonal contraceptives should be conducted.

5. Safety information should be incorporated into the training materials for grass roots family planning providers, so that they can provide a more informed choice of contraceptives and reproductive health service to reduce the incidence of ADRs among women taking contraceptives.

Key words: combined oral contraceptives, intrauterine device, stroke, prospective cohort study, case control study, hypertension, hyperlipemia

Cancer Phobia and Hormonal Contraception

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Since the introduction of oral contraceptives in 1960, there have been concerns whether use of hormonal contraception is associated with cancer. The majority of the epidemiological studies addressing this issue have been with combination oral contraceptives; a few studies have examined depot medroxyprogesterone acetate (DMPA). There are very limited or no data on newer methods such as the levonorgestrel-releasing intrauterine device (LNG-IUD), the contraceptive vaginal ring, or contraceptive transdermal patch. Today we will focus on breast cancer, cervical cancer, ovarian cancer, endometrial cancer, and colon cancer.

Breast Cancer

In 1996, a collaborative project representing a meta-analysis of the better epidemiologic studies in the literature was published.[1] A total of 54 studies were included in the analysis representing 53,297 women with breast cancer and 100,239 control subjects. About one-third of the cancers were diagnosed in women younger than 45 years of age and about one-half after 1985. Thus, the data probably provides clinicians with the best information that can be applied to their current oral contraceptive users. The relative risk of breast cancer for current users of oral contraceptives compared to never-users was 1.24. This small increase in risk persisted for about ten years, with disappearance of the risk after that time period. In addition, there was no overall effect of oral contraceptive use by dosage, specific formulation, duration of use, age at first use, age at time of cancer diagnosis, or by family history of breast cancer. The comparison of ever-users of oral contraceptives with never-users revealed that the relative risk for tumors that had spread as opposed to localized disease was 0.88. This suggests that although oral contraceptive users face a modest increase in risk of breast cancer, the disease tends to be localized. The pattern of disappearance of risk after ten years coupled with the tendency towards localized disease suggests that the overall effect may represent detection bias or perhaps a promotional effect. More recent information from a case-control study suggests that most users of oral contraceptives may have no substantial increase in the risk of breast cancer.[2, 3] This population-based study from five metropolitan areas across the United States included women between 35 and 64 years of age and involved 4575 breast cancer subjects and 4682 control subjects. In this study, the relative risk of breast cancer was 1.0 (95 % CI 0.8, 1.3) among current users of oral contraceptives and 0.9 (95% CI 0.8, 1.0) for former users. The relative risk did not show any consistent

increase by duration of use or with higher estrogen doses. No increase in risk was noted for women with a family history of breast cancer or for women starting oral contraceptive use at an early age. Finally, there were no differences in risk noted between white and black women. Thus, this study indicates no increase in risk of breast cancer associated with oral contraceptive use particularly later in life where the risk is highest. Studies examining subgroups of women at high risk, e.g. BRCA carriers or those with a family history of breast cancer, have failed to demonstrate an increased risk of breast cancer if these women use oral contraceptives.[4, 5] The risk of breast cancer among DMPA users appears to be minimal if it exists at all.[6, 7] Postmarketing data of users of the LNG-IUD does not show evidence of an increased risk of breast cancer in women age 30-54 years.[8]

Cervical Cancer

A number of studies suggest that oral contraceptives are associated with an increased risk of cervical cancer especially in women with evidence of human papillomavirus (HPV) infections. For example, a World Health Organization (WHO) expert panel in 2002 concluded that any increased risk of cervical cancer associated with oral contraceptive use occurred with long-term use among women with persistent HPV infection.[9] They also pointed out that even though there was an increased risk in this subset of women, most women with HPV infection do not develop cervical cancer. Similarly, a meta-analysis of 28 studies concluded that risk of cervical cancer among oral contraceptive users was related to duration of use.[10] Among users of oral contraceptives of less than five years, the relative risk of cervical cancer was 1.1, 95% confidence interval 1,1,1.2 while for users of ten or more years the relative risk was 2.2, 95% confidence interval 1.9,2.4. Risks were roughly the same for squamous and adenocarcinomas as well as for in situ and invasive disease. The risk in recent studies appears highest among women with evidence of HPV infection and increasing duration of oral contraceptive use.[11, 12]. There is no data linking the LNG-IUD to an increased risk of cervical cancer. Several studies have found no increased risk of this cancer among users of DMPA.[6, 13]

Endometrial Cancer

Multiple case-control studies and cohort studies have demonstrated that use of oral contraceptives conveys protection against endometrial cancer.[14-16] Overall, there is up to a 50% reduction in risk which begins about one year following initiation of use. Protection appears to increase with duration of use and persists up to 20 years after oral contraceptive use is discontinued. The strength of the protective effect varies in studies for women with potential risk factors such as obesity and nulliparity. The purported protective mechanism of action is a reduction in the mitotic activity of endometrial cells by the action of the progestin component of oral contraceptives. DMPA use reduces the risk of endometrial cancer by about 80% compared to non-use.[17] There is limited data on the relationship of the LNG-IUD and endometrial cancer, which suggest the effect is protective.[18, 19]

Ovarian Cancer

Multiple case-control and cohort studies have shown a protective effect for oral contraceptives against the development of ovarian cancer.[20-23] Overall, there appears to be between a 40 to 80% overall decrease in risk among users with protection beginning about one year after initiating use and conveying about a 10-12% decrease in risk for each year of use. Protection persists for 15 to 20 years after one has discontinued use of oral contraceptives. The mechanisms by which oral contraceptives may produce this effect include suppression of ovulation resulting in a reduced frequency of "injury" to the ovarian capsule and the suppression of gonadotropins. A recent theory based on a primate model suggests that induction of ovarian apoptosis which in turn eliminates surface epithelium inclusion cysts may play a role in reducing ovarian cancer risk among oral contraceptive users.[24] Ovarian cancer risk is not altered by use of DMPA.[25] There is no data related to the use of the LNG-IUD.

Colorectal Cancer

A reduction in the risk of colorectal cancer is another area of potential benefit to oral contraceptive users. A large meta-analysis has suggested an 18% reduction in risk for ever-users of oral contraceptives compared to never-users.[26] However, there have been at least three studies that suggest up to a 40% reduction in colon and rectal cancer among women who have ever used oral contraceptives.[27-29] Further, a recent analysis from the Women's Health Study also indicated a 33 to 40% reduction of colorectal cancer risk among ever users of oral contraceptives.[30] However, one other study demonstrated no effect with oral contraceptive use.[31] Potential mechanisms of action include reduction of bile acid production, estrogen receptors protecting against development of the cancer, and oral contraceptives reducing the development of adenomatous polyps.[32] There are no data on DMPA or LNG-IUD use and the risk of colorectal cancer.

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