



Updates on Hormonal Contraceptives

Dr. Sue ST LO

MBBS, FRCOG, MPA

The Family Planning Association of Hong Kong



Dr. Sue ST LO

This article highlighted some important safety updates on two modern hormonal contraceptives and introduced four hormonal contraceptives that were launched in Hong Kong in the past three years.

Safety of Evra® (Janssen Pharmaceutica, Hong Kong)

In 2001, Ortho Evra® patch was approved by the United States Food and Drug Administration (US FDA) for contraception. Each patch contains 0.75mg ethinyloestradiol and 6mg norelgestromin. Evra® was launched in Hong Kong in 2003 and it contains 0.6mg ethinyloestradiol and 6mg norelgestromin. Both Ortho Evra® and Evra® releases approximately 20µg of ethinyloestradiol and 150µg of norelgestromin into the systemic circulation daily.

It is a reliable contraceptive with Pearl index 1.24 (95% CI, 0.19-2.33), which is similar to that of a triphasic combined oral contraceptive (COC) pill (2.18; 95% CI, 0.57-3.8)¹. However, its safety has remained a main concern after reports on venous thromboembolism (VTE) in Ortho Evra® users emerged. In November 2005, the US FDA announced a revision in the Ortho Evra® label to include a bolded warning on the higher exposure to oestradiol. It stated that the average concentration for ethinyloestradiol at steady state was approximately 60% higher in women using Ortho Evra® than in women using 35µg ethinyloestradiol COC. The higher oestrogen exposure might increase risk of adverse events but there was insufficient evidence to associate VTE with the use of Ortho Evra®².

In September 2006, US FDA announced an update to the Ortho Evra® label to reflect the risk of VTE with patch use³. The first study⁴ cited in this update was a nested case-control study based on information from a company that collected and organised information on claims paid by managed care plans. It did not show any increased risk of nonfatal VTE in patch users compared with women using 35µg ethinyloestradiol and norgestimate COC. The overall incidence of nonfatal VTE was 52.8 / 100,000 women-years (95% CI, 25.8 - 74.9) among Ortho Evra® users and 41.8 / 100,000 women-years (95% CI, 29.4 - 57.6) among women using COC. The odds ratio of VTE for current Ortho Evra® users was 0.9 (95% CI, 0.5 - 1.6) compared with COC users. There were no data on fatal VTE, as the company did not capture deaths that occurred outside a health care facility. The second study⁵ cited in this update was a retrospective review of clinical records. It showed a two-fold increase in medically verified VTE in Ortho Evra® users compared with 35µg ethinyloestradiol COC users (OR 2.4; 95% CI, 1.1-5.5). The most recent label revision⁶ in January 2008 quoted

findings from the third study⁷ that showed an insignificant two-fold increase risk of VTE in Ortho Evra® users compared with women using 30µg ethinyloestradiol COC (OR 2.0; 95% CI, 0.9-4.1).

There are no data on the risk of VTE with Evra®. Since Evra® releases similar amount of ethinyloestradiol into the circulation everyday as Ortho Evra®, the risk should be similar.

In an earlier study, Ortho Evra® users were found to have significantly more breast discomfort and dysmenorrhoea than women using triphasic COC and there were significantly more women who discontinued patch because of headache and dysmenorrhoea⁸. There are no data regarding the risk of cervical or breast cancers with patch use.

Revised Duration of Use for Diane 35® (Bayer HealthCare Ltd, Hong Kong)

In Hong Kong, Diane 35® is a prescription drug licensed for the treatment of androgen dependent diseases in women and for contraception. In the United Kingdom, the Committee on Safety of Medicines and the Medicines Control Agency⁹ recommended against using it for the sole purpose of contraception because of a four-fold increase in the risk of VTE compared with second generation COC¹⁰. It is indicated for the treatment of severe acne that does not respond to oral antibiotics and moderately severe hirsutism and it should be discontinued 3-4 months after these androgen-related symptoms resolved⁹.

An Extensively Studied Monthly Injectable -- Cyclofem® (Concept Foundation, Bangkok, Thailand)

This monthly injectable contains 5mg oestradiol cypionate and 25mg medroxyprogesterone acetate. It had been extensively studied by the World Health Organization and was approved by US FDA for contraception in October 2000. It was introduced to Hong Kong in 2007 by the Concept Foundation, which is a non-profit foundation established by the UNDP/UNFPA/WHO/WB Special Program in Reproductive Health (WHO/HRP), PATH and the World Bank in 1989.

Cyclofem® is highly effective with a first-year failure rate of less than 0.2%^{11,12}. Short-term studies showed little effect on haemostasis, coagulation, lipid metabolism, carbohydrate metabolism and liver function compared with COC¹³⁻¹⁶.

There were few epidemiological data on its long-term



side effects. Menstrual problems like irregular bleeding, prolonged bleeding, heavy bleeding and amenorrhoea were reported during the first few months. After that, women could expect regular and predictable monthly cycles, similar to COC use¹⁷. The contraceptive effects reversed relatively quickly following discontinuation and ovulation had been observed as early as 63 days after the final injection¹⁸. Cumulative conception rates following discontinuation were similar to that observed with COC¹⁹. Other side effects included weight change, breast tenderness, mood swings, acne, and nausea. In most cases, these side effects subsided with time and were not major reasons for discontinuation. In one trial, the 12-month method-related discontinuation rate for Cyclofem[®] was below 30%, which was comparable to 32% during the first year of COC use and substantially lower than 44% during the first year of DepoProvera[®] use²⁰.

A New Progestogen-only Pill -- Cerazette[®] (Schering Plough, SOL Ltd. Hong Kong Branch)

Cerazette[®] is a progestogen-only contraceptive pill (POP) that contains 75µg desogestrel. It offers more consistent ovulation inhibition (up to 97% of cycles) than levonorgestrel POP (up to 71% of cycles) thus has higher contraceptive efficacy (Pearl index: 0.4 vs 1.6 for levonorgestrel POP)²¹ and wider missed pill margin (12 hours instead of 3 hours for levonorgestrel POP)²². Ovarian ultrasound monitoring showed follicular diameter reduced with Cerazette[®] use over time and there were fewer large follicles (>30mm in diameter) compared to levonorgestrel POP users²¹.

The most common undesirable effect reported in clinical trials was irregular bleeding but the discontinuation rate due to abnormal bleeding pattern was similar to levonorgestrel POP²³. After a few months, bleedings would be less frequent and shorter. After 12 months of use, 50% of users had amenorrhoea or infrequent bleeding over a three months period, 40% had 3-5 bleeding or spotting episodes and 10% had more than six bleeding or spotting episodes or prolonged bleeding and spotting²⁴. Other reported side effects include acne, mood changes, breast pain, nausea and weight increase.

There are still some uncertainties about this new POP. The use of COC containing desogestrel is associated with an increased risk of VTE compared with levonorgestrel containing COC. However, the clinical relevance of this finding for desogestrel POP is unknown. Although use of Cerazette[®] is associated with a low estradiol serum level close to that of early follicular phase, it is as yet unknown whether this will have any clinically relevant effect on bone mineral density. There is no information on how long after stopping Cerazette[®] fertility will return.

A New COC -- YAZ[®] (Bayer HealthCare Ltd, Hong Kong)

YAZ[®] contains 24 active pills (20µg ethinylloestradiol / 3mg drospirenone) and four placebo pills. It has obtained US FDA approval for use as a contraceptive, for treatment of emotional and physical symptoms of premenstrual dysphoric disorder in women desiring contraception and for treatment of moderate acne. The Pearl index is 0.72 (upper limit of the 95% confidence interval, 1.69)²⁵.

The number of active pill is increased by three to compensate for the weaker ovarian suppression with ultra low dose ethinylloestradiol. Ovulation-inhibition study confirmed that the 24/4 formulation provided more consistent suppression of endogenous oestradiol and hormone fluctuations thus was more effective in inhibiting ovulation, even when 3 pills were missed at the start, than the 21/7 formulation²⁶. The cycle control by YAZ[®] was acceptable. In one study²⁵, 0.7% of women discontinued YAZ[®] because of irregular bleeding, which was lower than that cited for other 20µg COC (6% and 13%)^{27,28}. The shorter pill free interval and steady hormone level also reduced the occurrence of minor side effects like headache, abdominal pain and breast pain²⁶. These are important predictors for discontinuation²⁹.

Theoretically, YAZ[®] should be safer as it contains 20µg ethinylloestradiol. However, this is difficult to prove as most of the vascular complications are uncommon in healthy young women thus requires very large sample size to demonstrate any difference. The risk of VTE with YAZ[®] is expected to be at least similar, if not lower than Yasmin[®] (30µg ethinylloestradiol / 3mg drospirenone). Post marketing surveillance of Yasmin[®] in Europe³⁰ and United States³¹ showed that the incidence of VTE was not greater than other COC.

The contraindications to YAZ[®] are the same as other COC plus predisposition to hyperkalaemia like renal insufficiency, hepatic dysfunction, adrenal insufficiency and medications that might increase serum potassium.

A New COC -- Loette[®] (Wyeth (HK) Ltd, Hong Kong)

This COC is a prescription drug because it is also licensed for the treatment of acne in women aged 14 and above. It contains 20µg ethinylloestradiol and 100µg levonorgestrel. The Pearl index is 0.88 with acceptable cycle control and good tolerability profile³². The adverse effects, contraindications, eligibility assessment, practice pattern is the same as other COC.

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