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Case Report

Pills-related severe adverse events: A case report in Taiwan

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ABSTRACT

Objective: To review and evaluate the potential adverse effects of these oral contraceptives (OCP) to overweight women.
Case Report: A 19-year-old college student, with a body mass index (BMI) of 35.2 kg/m^2, who received 2 months of OCP containing cyproterone and ethinyl estradiol for polycystic ovary syndrome (PCOS)-related menstrual problems was complicated with a thromboembolism-related life-threatened disease. After intensive care, including the use of an extracorporeal membrane oxygenation system, thrombolytic treatment, anticoagulant, and inferior vena filter, she recovered well without significant sequelae.
Conclusion: This case illustrates the risk of using OCPs, especially for those containing cyproterone and ethinyl estradiol components, as a treatment for menstrual problems in young women with PCOS and a high BMI.

Introduction

Abnormal uterine bleeding (AUB) and its subgroup, heavy menstrual bleeding is a significant and common clinical entity affecting more than 10% of women of reproductive age [1], leading to a debilitating health outcome, reduced health-related quality of life, and a considerable economic burden on the health care system [2]. To clearly demonstrate AUB, there are nine main categories, arranged according to the acronym PALM-COEIN (polyp, adenomyosis, leiomyomas, malignancy, hyperplasia-coagulopathy, ovulation dysfunction, endometrial disorders, iatrogenic causes, and not-yet-classified entities), which help physicians and patients to deal with their clinical problems [2]. Medical treatment is one of the most important and popular therapeutic choices in the management of women with AUB or heavy menstrual bleeding, regardless of what categories were met [3]. Many agents can be applied, but hormone therapy may be the most popular, not only for decreasing the amount of menstruation, but also for regulating menstrual periods. The current options of hormone therapy mainly contain estrogen or progestins, either independently or in combination [i.e., combined oral contraceptives (OCPs)] [1]. Previous studies have shown that in more than 70% of the cases in which women received this treatment, the bleeding was stopped effectively [4].

Polycystic ovary syndrome (PCOS) is the most common hormonal abnormality syndrome of women of childbearing age [5]. Because irregular uterine bleeding caused by anovulation and hyperandrogenic status is one of the most apparent symptoms of PCOS [6], as well as many additional benefits of OCPs which have been reported, including decreased dysmenorrhea, decreased blood loss, ovarian cancer prophylaxis, and decreased androgens [7], it is the rationale to use OCPs in the management of these women with PCOS. However, women with PCOS have a 1.5 times higher baseline risk of venous thromboembolism (VTE) and a 3.7-fold greater effect with OCP use compared with non-PCOS women [8], but this is rarely emphasized. The following might be

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the first well recognized case report in Taiwan, which showed that PCOS was complicated by OCP-related severe VTE.

Case Report

A 19-year-old female, with a body mass index (BMI) of 35.2 kg/m^2, was diagnosed with PCOS at Taipei Medical University Hospital by clinical symptoms, gynecological ultrasound, and serum examinations in January 2015. She presented typical symptoms of PCOS, including oligomenorrhea, irregular cycles and persistent vaginal bleeding off and on, insulin resistance, and typical ultrasound finding of PCOS [9] since April 2015. Low dose hormone therapy, including medroxyprogesterone acetate (5–10 mg), estrogen (2–4 mg), and ergometrine maleate (0.6 mg) was prescribed at first, but symptoms persisted. In addition, this young woman could not tolerate the higher doses of hormone therapy. Finally, OCPs (Diane-35, cyproterone 2 mg, and ethinyl estradiol 0.035 mg, Bayer Weimar GmbH und Co. KG, Weimar, Germany) were suggested and prescribed on April 25.

The patient responded well at the first course, although she experienced right lower leg pain and swelling at the second course of OCPs (June 3). She did not care too much and did not report it to the doctors. On June 11, she lost consciousness suddenly and was brought into the hospital where an electrocardiogram showed pulseless electrical activity. After 1 hour of cardiopulmonary resuscitation, vital signs were still unstable and she did not recover consciousness. Therefore, extracorporeal membrane oxygenation was set up. Chest computed tomography showed multiple filling defects within the bilateral pulmonary arteries, favoring the diagnosis of pulmonary embolism. The electrocardiogram reported right heart enlargement. Serum D-dimer was 25.49 ug/mL. Thrombolytic treatment was given immediately. Extracorporeal membrane oxygenation was removed on June 15. She stayed in the intensive care unit and was transferred to a ward on June 19. An inferior vena cava filter was placed in order to prevent further life-threatening episodes on June 21. She was discharged on June 30, 2015 when her general condition was stabilized. She recovers well without sequelae at the date of this report, although oral anticoagulant therapy is continuous.

Discussion

Diane-35/Dianette, which contains ethinylestradiol (35 μg) and cyproterone acetate (2 mg), provides effective birth control, but is not indicated as an OCP and is approved only as therapy for androgen-sensitive skin conditions [10]. However, many physicians may be unaware of concerns about the drug's safety profile and the fact that it is not approved for use solely as an OCP [10]. Although a Danish study showed no difference in risk of VTE between levonorgestrel and cyproterone users [11], a UK study (100,000 women) showed a significant four-fold increase of VTE [12]. While there have been reports of VTE with fatal outcomes after the use of Diane-35 in the Netherlands, France, and Canada, which elevated attention to drug safety and led to the suspension of the drug in France [9,13,14], there are no previous reports in Taiwan or in any other Asian countries.

To report this case, we used the term "cyproterone, ethinylestradiol, and Asia" (from 1956 to March 15, 2016) to search PubMed for relevant English-language articles (http://www.ncbi.nlm.nih.gov/pubmed/?term=cyproterone%2C+ethinylestradiol%2C+Asia) and found seven published articles for this topic. However, none of the articles showed the severe side effects similar to those in our report. This case illustrates the risk of using OCPs containing cyproterone as a hormonal treatment for AUB in young women, particularly in women with PCOS and a high BMI. However, is the fatal risk of OCPs really related to cyproterone components? Vasilakis-Scaramozza and Jick [12] described a total of 128 women (cases and controls) who had used levonorgestrel-containing OCPs and 42 women (cases and controls) who had used cyproterone acetate-containing OCPs, and found that only 7% of the former group had used the preparation for 6 months or less, whereas 29% of the latter group had used the OCPs for 6 months or less, suggesting that there is a greater probability of first-time use; thus, the proportion of women using OCPs for the first time appears to have been higher in the cyproterone acetate-containing OCPs group, which contributed to some or all of the greater risk of VTE in that group [15]. The patient in the current report was also a first-time user and developed pulmonary embolism within 2 months, the most risky period to develop the severe thromboembolic events. Therefore, OCPs prescribed for any first-time users should be carefully evaluated and discussed. The balance of risks and benefits should always be taken into consideration to minimize the occurrence of catastrophic events.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Ethics approval

The research protocol was approved by the Taipei Medical University Joint Institutional Review Board (TMUJIRB N201512005).

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