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Updated Insights on the Risk of Venous Thromboembolism Associated with Combined Oral Contraceptives in the Japanese Population

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ABSTRACT

Combined oral contraceptives (COCs) are widely utilized among women for contraception and the management of menstrual disorders such as dysmenorrhea and hypermenorrhea. However, venous thromboembolism (VTE) remains an inherent adverse effect of COC usage, with numerous studies worldwide demonstrating an increased risk associated with these medications. Early signs of thrombosis can facilitate timely intervention. Healthcare professionals prescribing or dispensing COCs must comprehensively communicate both the benefits and potential risks of thromboembolism, along with pertinent clinical manifestations.

Introduction

COCs are not only highly effective in preventing pregnancy [1,2] but also provide significant therapeutic benefits in managing menstrual disorders, including alleviation of dysmenorrhea and reduction in menstrual flow. The non-contraceptive advantages of hormonal combination therapy can be categorized into three primary domains. First, COCs mitigate menstrual cycle-related symptoms such as dysmenorrhea, hypermenorrhea, and premenstrual syndrome [3,4]. Second, they aid in the treatment of gynecological pathologies, including adenomyosis and endometriosis, along with their associated complications [5,6]. Third, they confer protective effects against conditions such as pelvic inflammatory disease, ectopic pregnancy, and ovarian cancer [7,8]. Due to their ease of administration, COCs are widely adopted. While mild side effects are common, they often resolve after continued use for three to four cycles or upon switching to an alternative formulation with a modified hormonal composition. Nonetheless, a significant concern is the potential development of venous thromboembolism (VTE).

Venous Thromboembolism

Thrombosis is a pathological condition characterized by the formation of intravascular blood clots (thrombi), which may occlude blood vessels. When a thrombus formed within a vein dislodges and travels through the circulatory system, it may obstruct pulmonary or cerebral vasculature, leading to life-threatening complications. A

well-known example is deep vein thrombosis (DVT) occurring during prolonged immobility, such as in long-haul air travel, commonly referred to as "economy class syndrome." In such cases, prolonged sitting, restricted movement, and reduced hydration contribute to venous stasis and clot formation. If the clot embolizes to the pulmonary vasculature, it results in pulmonary embolism, severely compromising respiratory function. The elevated risk of VTE associated with COC use is attributed to the prothrombotic properties of estrogen and progestin [7-10]. Estrogen, in particular, enhances coagulation, predisposing individuals to thrombotic events. Epidemiological studies indicate that VTE incidence among COC users ranges from 3 to 9 cases per 10,000 person-years, compared to 1 to 5 cases in non-users [11,12]. Furthermore, the risk of thromboembolism peaks within the initial 90 days of COC initiation, accounting for approximately 53% of cases [11,12]. Statistically, the risk of VTE associated with COCs is comparable to the likelihood of a licensed driver being involved in a traffic accident in Japan, which is estimated at approximately 4 to 5 per 10,000 individuals annually [13]. During pregnancy, endogenous estrogen and progesterone levels increase substantially, persisting postpartum. Consequently, the incidence of VTE is estimated at 5 to 20 cases per 10,000 person-years during pregnancy and escalates to 40 to 65 cases per 10,000 person-years during the puerperal period (within 12 weeks postpartum) [14,15]. This suggests a significantly higher thrombotic risk during pregnancy compared to COC use, likely due to physiological adaptations aimed at minimizing hemorrhagic complications during childbirth.

Early Diagnosis of VTE

Thrombosis presents with early clinical signs, including lower limb swelling, localized pain, erythema, chest pain, dyspnea, headache, visual disturbances, and abdominal discomfort. If these symptoms emerge, immediate cessation of COC use and prompt medical consultation are imperative. The diagnosis of DVT involves biomarkers such as D-dimer, thrombin generation markers, Factor VIII, leukocyte count, and inflammatory cytokines. However, these markers are not entirely specific and may indicate other pathological conditions, including infections, inflammation, and cardiovascular diseases. Thus, the development of highly sensitive and specific biomarkers is essential for improved screening and early diagnosis of thromboembolism [16]. Given that the highest risk of thrombotic events occurs within the first four months of COC use, while discontinuation restores baseline risk within three months, vigilance in monitoring early symptoms is critical for mitigating adverse outcomes.

Conclusion

Physiologically, clot formation is a protective mechanism for vascular repair; however, under certain conditions, pathological thrombosis can occur [17]. While thrombi typically undergo fibrinolysis when no longer needed, risk factors such as smoking and hypertension—both of which exacerbate endothelial damage—preclude the safe use of COCs [17]. The primary risk factors for VTE include advanced age (>40 years), obesity, smoking, and hypertension (Table 1) [18-24]. To maximize the therapeutic benefits of COCs while minimizing the risk of thromboembolic complications, users must remain vigilant for any physiological changes during treatment and seek timely medical evaluation if concerning symptoms arise.

Table 1: Reported risk factors for thromboembolism associated with combined oral contraceptives.

Risk Factors	Ref.
Obese	[18,19]
Aged over than 40 years	[18,19]
Smoking	[20]
Hypertension	[21]
Hyperlipidemia	[21,11]
Family history of VET and thrombophilia	[22]
Cancer-bearing	[22]
Polycystic ovary syndrome	[23]
Autoimmune disease	[11,24]
Antiphospholipid syndrome	[24]

Conflict of Interest

The authors declare that they have no conflict of interest.

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