GENERAL GYNECOLOGY

Common iliac vein stenosis: a risk factor for oral contraceptive-induced deep vein thrombosis

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OBJECTIVE: The objective of the study was to determine whether women with significant left common iliac vein stenosis who also use combined oral contraceptives (COCs) have a combined likelihood of deep vein thrombosis (DVT) greater than each independent risk.

STUDY DESIGN: This was a case-control study comparing 35 women with DVT against 35 age-matched controls. Common iliac vein diameters were measured from computed tomography and magnetic resonance imaging. Logistic regression modeling was used with adjustment for risk factors.

RESULTS: DVT was associated with COC use ($P = .022$) and with increasing degrees of common iliac vein stenosis ($P = .004$). Compared with women without venous stenosis or COC use, the odds of DVT in women with a 70% venous stenosis who also use COCs was associated with a 17-fold increase ($P = .01$).

CONCLUSION: Venous stenosis and COC use are independent risk factors for DVT. Women concurrently exposed to both have a multiplicative effect resulting in an increased risk of DVT. We recommend further studies to investigate this effect and its potential clinical implications.

Key words: deep vein thrombosis, iliac vein, oral contraceptive, venous stenosis

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Combined oral contraceptives (COCs) are used by more than 100 million women worldwide.[1] According to the 1995 National Survey of Family Growth, approximately 1 in 5 American women between the ages of 15 and 44 years were using COCs, and 82.4% had used them at some point in their lifetime.[2] Although COCs are an effective means of birth control, their use have been associated with several risks. Various observational studies over the last several decades have reported an increased risk of deep vein thrombosis (DVT) in patients after starting COCs.[3] Without COC use, the baseline risk of DVT in normal, healthy women aged 15-44 years is approximately 1-3 cases per 10,000 person-years. In the first year of COC use, the risk of DVT increases by 3- to 6-fold.[4]

Given the small absolute risk of DVT in nonpregnant, reproductive-age women, screening strategies to identify who is at greatest risk for DVT prior to starting COCs are currently not recommended.[5] However, women who possess an underlying thrombophilia can experience exacerbation of their prothrombotic state during COC use. Studies focusing on factor V Leiden mutations and deficiencies in protein C, protein S, and antithrombin have established an additive risk of COC use in contributing to DVT in these patients.[6,7] However, these studies have not investigated the anatomic stasis component of Virchow's triad as an added risk factor for DVT, which we believe is important in the development of venous thrombus among women using COCs.

Currently, the clinically accepted definitions of venous stasis include recent travel and lower-extremity immobility.[8] However, reduced venous velocity can also occur because of anatomically narrowed vasculature that may impede flow. Cadaveric studies by May and Thurner[9] described naturally occurring compression of the left common iliac vein (LCIV) against the lumbar spine by the overlying right common iliac artery resulting in slow turbulent flow through the vein. This May-Thurner syndrome or iliac vein compression syndrome (IVCS) has been associated with ipsilateral DVT, especially those involving the proximal venous segments. Anatomic studies have shown that an underlying stenosis (>50%) of the LCIV is present in 22-24% of the healthy population.[9,10]

It is likely that the risk of DVT increases with the degree of venous stenosis. This hypothesis is supported by a study showing that patients with left iliofemoral DVT had a 74% mean stenosis of the LCIV compared with a 28% mean stenosis in an age-matched asymptomatic control group.[11] We have previously reported that 84% of COC-induced lower extremity DVTs occurred in the left leg, and in these patients there is an iliac vein mean stenosis of 71%.[12] Similarly, studies of acute DVT during pregnancy demonstrated that approximately 90% of pregnancy-induced DVTs oc-

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curred in the left lower extremity, with a propensity also toward the proximal veins.[13,14]

Therefore, we hypothesized that significant LCIV stenosis could be a risk factor for a first-time DVT episode in young women taking COCs. The goal of our study was to determine whether COC users with LCIV stenosis are at a higher risk for left-sided DVT than those without venous stenosis and, if so, to what degree.

Materials and Methods

A retrospective case-control study was conducted at an academic hospital under institutional review board approval. Hospital records from Jan. 1, 2002, to Dec. 31, 2008, were searched to identify women between the ages of 18 and 45 years who were diagnosed with DVT using *International Classification of Diseases*, ninth revision (ICD-9) codes (451.1, 451.2, 453.41, 453.40). Cross-sectional imaging was necessary for venous stenosis measurements, and all patients without computed tomography (CT) or magnetic resonance (MR) imaging of the lower abdomen or pelvis were excluded.

The case subjects were defined as those with a first-time, acute presentation of a lower-extremity DVT that was visually confirmed by ultrasound, CT, or MR imaging. Exclusion criteria were then used to minimize misclassification of outcomes within these case subjects. Patients were excluded if no DVT was found on imaging or if they had a history of chronic venous disease or previous lower-extremity surgical or endovascular vascular procedures that may have distorted the iliac vein anatomy. Furthermore, because nearly all cases of IVCS occur on the left, only subjects with unilateral left-sided DVT were included.

The control subjects consisted of women between the ages of 18 and 45 years who presented to the emergency room from January 2002 to December 2008 with a chief complaint of abdominal pain (ICD-9 codes 789.01-789.09) and who were evaluated with CT imaging of the abdomen and pelvis. Subjects were excluded from the control population if they had a prior history of DVT or lower-extremity surgical or endovascular procedure.

The electronic medical record for all subjects was reviewed to assess whether combination oral contraceptives were used at the time of presentation. Patients using any form of progestin-only or nonhormonal contraceptives were considered as nonusers of COCs. Additional prothrombotic risks were also identified, including smoking, active malignancy, pregnancy, self-described inherited thrombophilia or that confirmed by hypercoagulability testing, and recent prolonged travel or immobilization. A patient with any of these risk factors was considered as having an additional hypercoagulable state in our statistical modeling.

CT scans were performed on either an 8 row or 16 row multidetectors (General Electric Medical Systems, Milwaukee, WI). MR imaging was performed on a 1.5-Tesla systems (General Electric Medical Systems) and included gradient-echo sequences and dynamic time-of-flight spoiled gradient-echo sequences. Axial CT and MR images of 5 mm thickness or less were reviewed, and the minor diameter of the LCIV measured at the point at which the right common iliac artery crosses anterior to the left iliac vein. The cross-sectional minor axis diameter of the right common iliac vein was measured 1 cm below the inferior vena cava bifurcation. Measurements were performed independently by 2 reviewers (K.T.C. and L.V.H.) who were blinded to the subject's clinical presentation. The percent stenosis was calculated by dividing the LCIV minor diameter by the right common iliac vein minor diameter then subtracting this percentage from 100.

Simplified assumptions were made to determine the sample size needed in this case-control study. Based on the population frequencies of 17.3% women using COCs and 20% with iliac vein compression, we calculated approximately 3.5% of the population would concurrently have both conditions. We hypothesized that stenosis-induced stasis would have a prothrombotic effect independent from COC-related thrombophilia, and therefore, the relative risks of DVT for COC use and significant venous stenosis would be multiplicative. Compared with the patient with no risk factors, prior studies have estimated COC use and significant venous stenosis increased the relative risk of DVT by 3 and 7, respectively, resulting in a combined relative risk of both factors to be 21 times above baseline. With these assumptions, we calculated a sample size of 17 subjects was necessary to detect a significant effect ($\alpha = 0.05, \beta = 0.20$).[15] We then conservatively doubled this sample size to include the first 35 cases and controls that met our inclusion criteria.

Statistical analysis was performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC). The likelihood of venous thromboembolism with the primary factors of COC use and venous stenosis was assessed using logistic regression models adjusted for age and a variable representing the presence of additional hypercoagulable states. The effect of venous compression on DVT was reported for each percent increase in stenosis. A subgroup analysis was also performed to compare the odds of DVT for patients with and without COC use and with and without a clinically significant amount of IVCS (defined as ≥70% stenosis, based the anatomical measurements from Oguzkurt et al[11] and Tye et al[12]). The odds ratios and 95% confidence intervals were calculated, and statistical significance was set at an alpha level of 0.05.

Results

Between 2002 and 2008, 131 women between the ages of 18 and 45 years were diagnosed with DVT and had appropriate CT or MR imaging at our academic hospital. Ninety-two patients (70%) had unilateral left-sided DVT. Case subjects were then randomly chosen until the first 35 cases were found who met the exclusion criteria. In the same 6 year period, 853 total control subjects presented to the emergency room with abdominal pain, from which 35 controls were picked randomly. These control subjects consisted of genitourinary (23%) and gastrointestinal (19%) diagnoses, motor vehicle accidents (13%), back injuries (6%), infections including postsurgical dehiscence