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Reversible Ischemic Colitis in Young Women Association with Oral Contraceptive Use

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Ischemic colitis, a condition of middle-aged to elderly patients, occurs uncommonly in younger persons. In this study, we describe the clinical and pathological features of 18 young adults (mean age, 29 years; age range, 17-39 years) with spontaneous ischemic colitis, 17 of whom were women. All presented with abrupt onset of severe, cramping abdominal pain followed by hematochezia. Colonoscopic visualization of the mucosa showed segmental hyperemia, friability, and erosion affecting the distal transverse colon (three cases), splenic flexure (three cases), descending colon (five cases), and sigmoid (seven cases). Mucosal biopsy documented superficial ischemic necrosis in seven patients; 11 patients had full-thickness mucosal necrosis with regeneration. Colonic mucosa proximal and distal to the ischemic segment was endoscopically normal in all patients and histologically normal in the eight patients in whom biopsies were obtained. All patients recovered with supportive care. Median duration of illness was 2.1 days (range, 1-4 days). Ten women (59%) were using low-dose estrogenic oral contraceptive agents, compared with the 1988 national average of 18.5% oral contraceptive users among females aged 15 to 44 years. The calculated odds ratio yielded a greater than sixfold relative risk for the occurrence of ischemic colitis among oral contraceptive users. In addition, four women not currently on hormonal contraceptive therapy had a past history of oral contraceptive use; the three remaining women were taking estrogen as replacement therapy after oophorectomy. In one patient, documented reversible ischemic colitis recurred on resumption of oral contraceptive use; four women reported symptoms and signs of recurrent ischemia but did not seek further medical evaluation. Our data indicate that transient colonic ischemia represents a form of acute seg-

mental colitis in young adults; before the 5th decade of life, spontaneous ischemic colitis is a disorder found almost exclusively in women and is associated with the clinical use of exogenous estrogenic agents.

Key Words: Colon—Ischemia—Ischemic colitis—Oral contraceptives.

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Sudden, transitory reduction in splanchnic blood flow to the large bowel may result in avascular necrosis of the colonic mucosa (3,38,49,50,58,62,63, 69,73,84). Manifested clinically by the abrupt onset of abdominal pain followed in short order by hematochezia or bloody diarrhea, reversible ischemic colitis resolves rapidly with restitution of the blood supply (10,11,32,57,73). In common with other forms of ischemic bowel disease, the incidence of reversible colonic ischemia increases with advancing age in parallel with the prevalence of its main predisposing condition, atherosclerosis (1,10,12,19, 57,58,73). Ischemic colitis occurs infrequently before the 5th decade of life; it typically affects young adults in the context of an overt, precipitating disorder, such as hypovolemic shock (71), vasculitis (16,44,45), or drug use (6,21,54,55,61,67,78,80,81, 85). In addition, right-sided hemorrhagic colitis caused by infection with *Escherichia coli* 0157:H7 may mimic the pattern of spontaneous ischemic colitis in young patients (28,29,39,65,70,72,75,81).

Since the first descriptions of thromboembolism associated with the use of oral contraceptive agents (9,36,40,68), exogenous hormonal contraception has been repeatedly implicated in the pathogenesis of ischemic colitis (4,5,20,23,24,26,27,33,35,41,46, 51,56,64,79,82), although a causal relationship has not been established. Anecdotal reports (5,20,26, 33,35,41,51,82), inclusion of patients with proximal

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hemorrhagic colitis (17,53), and sole reliance on roentgenologic evaluation (15,24,41,53,76) all have confounded efforts to confirm a role of oral contraceptive use in the causation of ischemic colitis. Over a 5-year period, we encountered 18 young adults, all women except one, in whom the clinical course, direct colonoscopic visualization, and biopsy histopathology documented segmental, left-sided, reversible ischemic colitis. In this report, we provide statistical validation for the often suspected association between exogenous hormonal therapy and ischemic colitis and estimate the magnitude of risk to women using oral contraceptives of incurring an episode of ischemic colitis.

MATERIALS AND METHODS

For the period of November 1987 through July 1993, the surgical pathology files of the Baptist Memorial Hospital, Memphis, Tennessee, recorded 35 patients under 40 years of age whose endoscopically obtained colonic mucosal biopsy samples were coded to ischemic colitis; reexamination of biopsies confirmed the diagnosis of ischemia in all cases. After initial review of clinical records, 17 patients were excluded from the study for the following reasons: one patient had stool culture-positive *E. coli* 0157:H7 hemorrhagic colitis affecting the ascending colon; one was profoundly hypotensive following a motor-vehicle-accident trauma; and 15 patients had endoscopic evaluation restricted to flexible fiberoptic sigmoidoscopy so that macroscopic evaluation of the entire colonic mucosa was not accomplished.

The final study population then consisted of 18 patients under the age of 40 years with ischemic colitis of undetermined etiology, all of whom had undergone complete visualization of the colonic mucosa via flexible fiberoptic colonoscopy. Follow-up data were available from physicians' office records, and 17 patients were personally interviewed by one of us (D.G.D.).

RESULTS

Clinical Findings

Table 1 presents selected clinical data for our young adults with spontaneous ischemic colitis. Of the 18 patients, 17 were women. They ranged in age from 17 to 39 years (mean and median ages, 29 years). Their clinical presentation was strikingly uniform. All experienced the sudden onset of severe, cramping abdominal pain localized to the left lower quadrant in five patients and to the midabdomen in three patients; the remaining 10 patients de-

TABLE 1. Clinical features of 18 young adults with reversible ischemic colitis

Age (yr)	
range	17-39
mean	29
Gender	
Female	17
Male	1
Symptoms	
abdominal pain	18
hematochezia	18
nausea	6
vomiting	3
Signs	
Afebrile	18
Abdominal tenderness	10
Laboratory data (no. tested)	
Anemia	0
Leukocytosis	5
Enteric pathogens (7)	0
Clostridium difficile (3)	0
Abdominal roentgenogram (4 patients tested)	Normal

scribed the abdominal pain as generalized. Intense pain, which in 13 patients commenced in the late evening to early morning (8:00 p.m. to 2:00 a.m.), persisted for 2 to 4 h and then waned and assumed a dull, aching quality. Six patients suffered associated nausea, in three patients accompanied by vomiting. Abdominal pain preceded the equally sudden appearance of hematochezia or frankly bloody diarrhea. In one patient, abdominal pain and passage of a maroon-colored stool were concurrent events. For the remaining 17 patients, the mean interval between onset of abdominal pain and efflux of bright red blood per rectum was 10 h (range, 15 min to 72 h).

Twelve patients presented to the emergency department, and six sought consultation directly with a gastroenterologist. On physical examination, all patients were afebrile; none was hypotensive. Compared with the intensity of pain, the abdominal examination was less impressive. All patients had normal bowel sounds. In 10 patients, tenderness to deep palpation was elicited. Hemoglobin and hematocrit values were within reference ranges in all patients; five patients had modest leukocytosis (range, 11,100 white cells/cmm to 19,100 white cells/cmm). Stool samples cultured from seven patients yielded no enteric pathogens. Clostridium difficile toxin assays performed in three patients were negative. Plain abdominal roentgenograms of four patients showed no abnormality.

Colonoscopic examination performed 9 to 84 h (mean, 35 h) after onset of abdominal pain disclosed alterations of the mucosae of all patients. Sharply segmental, confluent, or patchy areas of mucosal hyperemia and friability were noted (19,22,32,52,

77). Mucosal erosions, when present, were irregular in configuration. Linear ulceration was not observed. In three patients, the endoscopic abnormality was confined to a short length of the distal transverse colon; mucosae of the splenic flexure, descending colon, and sigmoid were affected in three, five, and seven patients, respectively (Fig. 1). The ascending colon, proximal transverse colon, and rectum of all patients were endoscopically normal.

Colonic Mucosal Biopsy Findings

In all patients, colonic mucosal biopsies sampled from endoscopically abnormal areas showed features that are characteristic of ischemic colitis (30, 31, 57, 58, 62, 66). Surface epithelium, together with variable depths of colonic mucosa, was sloughed. Necrotic debris formed a band-like membrane, under which cuboidal or flattened, mucin-depleted goblet cells exhibited an increased nuclear-cytoplasmic ratio reflective of regeneration (Fig. 2). The superficial lamina propria assumed the homogeneous, eosinophilic appearance of coagulative necrosis; the deep lamina propria was edematous. In-

flammatory cells consisting exclusively of polymorphonuclear leukocytes infiltrated the mucosa. Capillary thrombi were not identified.

In seven cases, the zone of ischemic necrosis was confined to the superficial portion of the mucosa; the remaining 11 cases contained foci of full-thickness mucosal necrosis (Fig. 3). Biopsies of endoscopically normal mucosae proximal and distal to the ischemic segment were also obtained from eight patients (cecum, two; ascending colon, three; transverse colon, three; descending colon, one; sigmoid, one; rectum, five); they showed either histologically normal colonic mucosa or lamina propria edema.

Risk Factors for Colonic Ischemia

All 18 patients were in good health. None gave a history of atherosclerosis or preexisting cardiac disorder. No patient correlated the ischemic episode with antecedent food ingestion. Although four patients acknowledged occasional use of nonsteroidal anti-inflammatory drugs, the bout of colonic ischemia was not temporally related to their administration. Recent antibiotic use was not a factor. No patient admitted to illicit drug use even during confidential questioning. Six women were cigarette smokers. None had endometriosis.

Among the 17 young women with spontaneous ischemic colitis, 10 (59%) were using exogenous hormonal therapy as their method of contraception compared with the 1988 national average of 18.5% oral contraceptive users among females aged 15 years to 44 years (59). Based on these data, the calculated odds ratio yielded a sixfold relative risk for incurring an episode of ischemic colitis among women using hormonal contraception (Fig. 4) (41). Duration of oral contraceptive use among these 10 women ranged between 1 and 72 months (median, 42 months) (Table 2). All were using combination oral contraceptives containing both progestational and low-dose estrogenic compounds, including norethindrone and ethinyl estradiol, levonorgestrel and ethinyl estradiol, and norethindrone and mestranol in eight, two, and one patients, respectively.

Among the remaining seven women, three were taking supplemental estrogen as replacement therapy following total abdominal hysterectomy and bilateral salpingo-oophorectomy. The four remaining women had used oral contraceptives continuously for 2, 4, 5, and 8 years but had discontinued their use 6 months to 20 years before suffering reversible ischemic colitis.

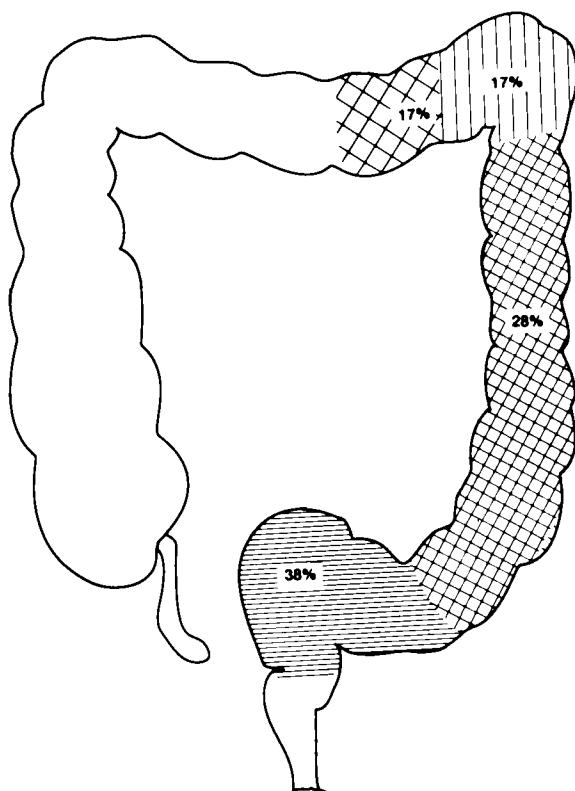


FIG. 1. Among 18 young patients with reversible, left-sided, segmental ischemic colitis, sites of involvement included the distal transverse colon ($n = 3$), left colic flexure ($n = 3$), descending colon ($n = 5$), and sigmoid ($n = 7$).

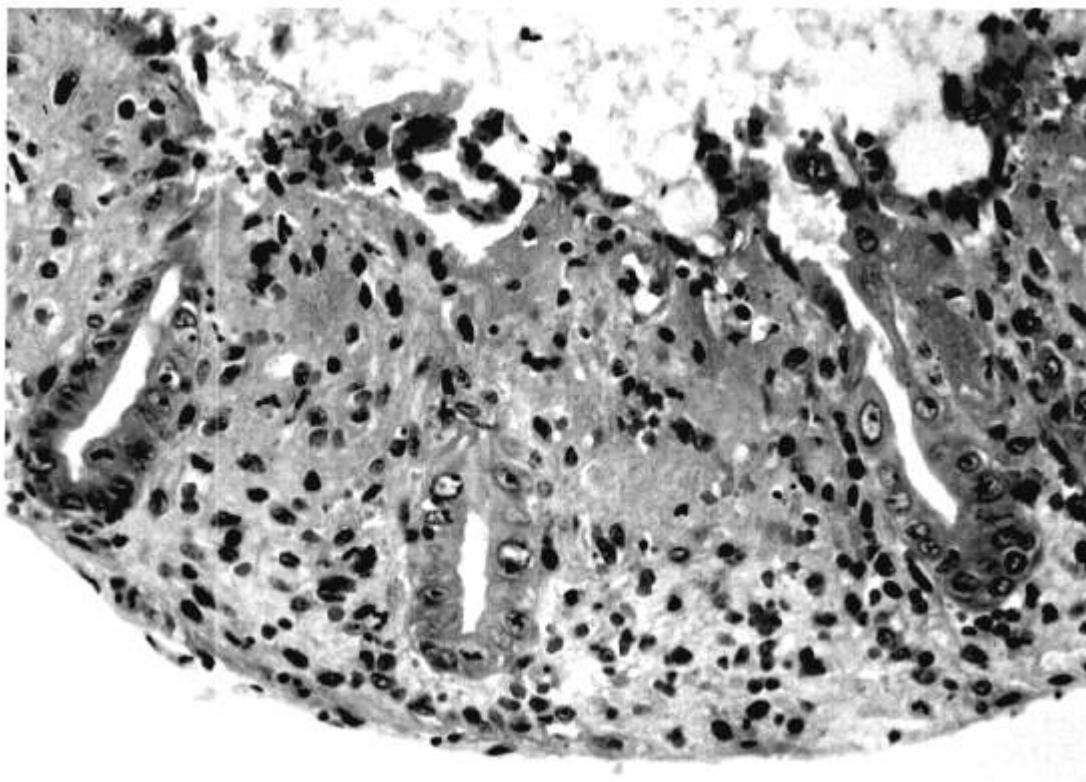


FIG. 2. This photomicrograph illustrates the histopathological appearance of reversible ischemic colitis as it presents in endoscopically obtained mucosal biopsy samples (Hollande's-fixed tissue). The surface epithelium is sloughed. An eosinophilic band-like zone of coagulative necrosis occupies the upper half of the mucosa. The so-called withering crypt appearance (66) is characteristic of mucosal ischemia (lumen at top).

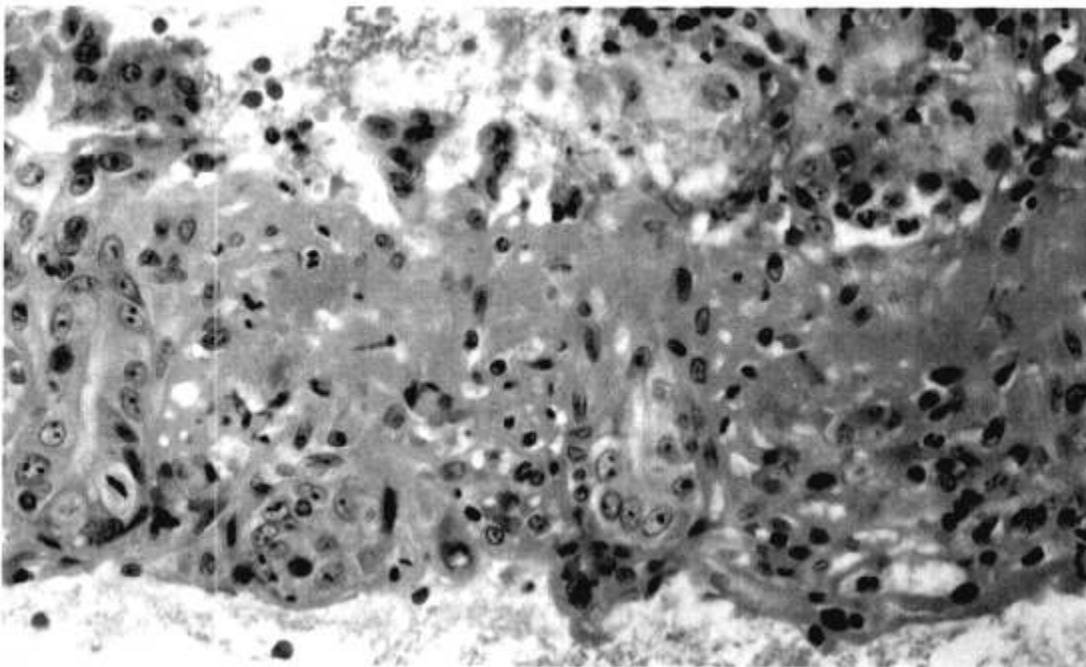


FIG. 3. More extensive ischemic injury of the colonic mucosa is depicted in this photomicrograph. To the right of the field is full-thickness mucosal necrosis (lumen at top).

Therapy and Follow-up Data

All patients received supportive care. Ten were treated with i.v. hydration; for the other eight patients, oral hydration and observation were elected. Symptoms resolved rapidly in all cases. The mean duration of illness was 2.1 days; no patient experienced persistence of symptoms for more than 4 days. Eight women have continued exogenous hormonal therapy. Five women discontinued oral contraceptive use; three resumed hormonal contraception 1.5 years, 2 years, and 2.5 years after suffering colonic ischemia.

Ischemic colitis confirmed by colonoscopic examination and mucosal biopsy recurred in one woman 20 months after the initial episode. The patient had continued oral contraceptive use after the first bout of colonic ischemia but discontinued hormonal contraception in the wake of the second attack; she has been free of recurrence for 34 months. Four women reported a recurrence of symptoms identical to those experienced during the documented incident of colonic ischemia. Despite severe abdominal pain and rectal bleeding, these patients relied on the self-limited nature of the initial event and did not seek medical attention; their symptoms resolved spontaneously. Thirteen patients denied symptoms of recurrent ischemic colitis 4 to 59 months (mean and median, 29 and 27 months, respectively) following the clinical episode of colonic ischemia.

DISCUSSION

Prior to the sixth decade of the 20th century, colonic ischemia signified solely transmural infarction of the large bowel (7,47,57,58,62). With description of ischemic ulcers and strictures of the colon came awareness of the potential for hindgut injury on the basis of chronic vascular insufficiency (1,7,12,15,

44,47,57). Transient ischemic colitis, wherein avascular necrosis confined to the mucosa is rapidly reversible, now rounds out the modern schema of ischemic bowel disease (1,11,30,31,47,58,62,73). In today's era of prompt interventional colonoscopy, transient ischemic colitis has emerged as the most common manifestation of colonic ischemia (11,12,19,73).

Reversible ischemic colitis follows a characteristic *modus operandi*. It is a disorder of older adults who frequently claim generalized atherosclerosis as a predisposing condition (1,10,11,19,32,57,58,66,73). Avascular necrosis is heralded by the abrupt onset of piercing abdominal pain; the slough of necrosed mucosa that ensues results in hematochezia. Although any segment of large bowel from cecum to rectum may be involved, transient ischemic injury has a predilection for affecting the left colon (1,11,12,13,44,46,58,62,73). Reversible colonic ischemia resolves with the rapidity with which it strikes. Except for their age, our 18 young adults with transient ischemic colitis conform closely to this classical scenario. The female predominance among young adults with ischemic colitis is not unique to our study. Barcewicz and Welch described 10 patients under the age of 50 years with colonic ischemia, of whom nine were women (4). Moreover, of the 15 patients excluded from our study due to incomplete endoscopic evaluation, 14 were women.

Although uncommon, ischemic colitis is not unheard of among young patients. A predisposing condition including hypovolemic shock (71), drug use (6,21,54,55,61,67,78,80,81,85), and vasculitis (16,44,45) is usually apparent. High on the list of etiological agents is *E. coli* 0157:H7, which in its most severe form may present a histopathological appearance reminiscent of ischemic colitis (18,28,29,

Oral Contraceptive Use			
	+	-	
Patients with Ischemic Colitis	10	7	
General Population	18.5	82.5	

$$= \frac{10/7}{18.5/82.5} = \frac{1.42}{0.225} = 6.31$$

FIG. 4. The estimated relative risk of developing ischemic colitis for oral contraceptive users is shown here. The general population refers to the percentage of females in the United States aged 15 years to 44 years (59). The odds ratio indicates a greater than sixfold relative risk for incurring an episode of ischemic colitis while using oral contraceptives (42).

TABLE 2. Oral contraceptive use among 10 women with spontaneous ischemic colitis

Patient No.	Duration of use (Mo)	Contraceptive agent ^a
1	36	Ortho-Novum 7/7/7
2	60	Tri-Levlen-21
3	72	Ortho-Novum 7/7/7
4	60	Ortho-Novum 1/50
5	3	Ortho-Novum 7/7/7
6	48	Ortho-Novum 1/35
7	3	Ortho-Novum 7/7/7
8	2	Ortho-Novum 7/7/7
9	1	Ortho-Novum 7/7/7
10	48	Triphasil-21, & Ortho-Novum 7/7/7

^a Ortho-Novum R, Ortho Pharmaceutical Corporation, Raritan, NJ, U.S.A.; Tri-Levlen R, Berlex Laboratories, Inc., Wayne, NJ, U.S.A.; Triphasil R, Wyeth-Ayerst Laboratories, Philadelphia, PA, U.S.A.

39,65,70,72,75,81). Enterohemorrhagic colitis invariably affects the proximal colon (18,28,39,70,75), shows no gender predilection, and may give rise to hemolytic-uremic syndrome (18,72,75); furthermore, watery diarrhea usually precedes the appearance of hematochezia (28,29), and the average duration of illness is 7 days (65). By contrast, the exquisitely segmental and rapidly reversible left-sided colonic ischemic injury in our patients is inconsonant with a manifestation of *E. coli* 0157:H7 infectious colitis.

Many investigators have linked oral contraceptive use to ischemic colitis in young women, although to date evidence in support of an association has been limited to case reports (5,20,24,26,33,35,41,46,51,64) and small series (4,23,27,79). Kilpatrick et al. initially described two patients with alleged oral contraceptive-induced ischemic colitis; in both women, barium enema showed exclusively right colonic involvement suspicious for *E. coli* 0157:H7 hemorrhagic colitis (41). Cotton and Thomas then called attention to the case of a 39-year-old obese cigarette smoker with a 2-year history of oral contraceptive use who suffered an episode of ischemic colitis affecting the splenic flexure and descending colon (20). Among seven patients with hormonal contraceptive-related ischemic bowel disease reported by Ghahremani, four had reversible ischemic colitis (27). During a review of 26 cases of spontaneous ischemic colitis, Barcewicz and Welch found 10 patients under the age of 50 years, four of whom were taking oral estrogen preparations (4). In describing five young women with estrogen-related abdominal pain and bloody diarrhea, Tedesco et al. adverted to the danger of misconstruing segmental ischemic colitis as Crohn's disease of the colon (79).

With our study, the long-suggested association between hormonal contraceptive use and the occurrence of ischemic colitis has received statistical validation. Among the 58 million females aged 15 years to 44 years living in the United States in 1988, 60% practiced contraception, via either contraceptive sterilization or other modalities (59); 18.5% opted for exogenous hormonal therapy as their contraceptive method of choice (59). There was no appreciable change in the percentage of oral contraceptive users between 1988 and 1990; contraceptive data for 1991–1993, the remaining years encompassed by our study, are not yet available (personal communication, Dr. William D. Mosher, Family Growth Survey Branch of the National Center for Health Statistics, Centers for Disease Control, U.S. Department of Health and Human Services, Hyattsville, MD, U.S.A.). By contrast, among our 17 fe-

male patients, 59% were using oral contraceptives at the time of their ischemic episode. The data are more compelling when age strata are considered. Among women aged 35 years to 39 years, the prevalence of both female and male contraceptive sterilization rises; only 11.6% use oral contraceptives (59). In addition to the 10 current oral contraceptive users, three of our patients were taking replacement hormonal therapy post-oophorectomy, and the remaining four women were former oral contraceptive users.

Some statistical aspects of the oral contraceptive-ischemic colitis association require closer scrutiny. Given the ideal putative scenario wherein each case in our series was matched with five controls randomly sampled from the population of American females aged 15 years to 44 years, the null hypothesis, that there is no association between oral contraceptive use and ischemic colitis, would be strongly rejected ($p < 0.005$). As our patients all resided in the Memphis metropolitan area, caution must be exercised in accepting national rates of oral contraceptive use for comparison. The exact prevalence of oral contraceptive use among women in the catchment population of the Memphis environs is unknown. However, even if the rate of oral contraceptive use among Memphians was 70% higher than that of their national counterparts, the odds-ratio would still indicate a greater than threefold relative risk for the occurrence of ischemic colitis among oral contraceptive users. The prevalence of oral contraceptive use in our catchment population would need be 300% in excess of the national average to extinguish evidence of excess risk (42).

Although statistical correlation does not ipso facto impute causality, in conjunction with scientific observations, it does advance the plausibility of a causal relationship between exogenous estrogenic activity and triggering of ischemic colitis. Distinctive endothelial and intimal hyperplasia of arteries and veins has been described in young women taking oral contraceptives (37). The increased incidence of thromboembolism among oral contraceptive users may relate to hypercoagulability induced by the estrogenic component of the compound (8, 25,60). Accelerated platelet aggregation, enhanced activity of clotting factors, and delayed fibrinolysis have been observed in patients taking estrogenic oral contraceptive agents (8,25,60). The circadian variation of fibrinolytic proteins—nocturnal dominance of blood concentrations of plasminogen activator inhibitor and concomitant paucity of plasminogen activator—may explain the frequent occurrence of ischemic colitis in the late evening and early morning hours among our patients (2). The

effects of estrogen on coagulation parameters are alleged to be dose dependent (8,9,36); however, all of our patients suffering ischemic colitis were using compounds containing low doses of estrogen, in accord with current contraceptive practice.

Despite the association between oral contraceptive use and transient ischemic colitis, our data do not support de facto cessation of oral contraceptive therapy among women suffering reversible colonic ischemia. Five of our patients reported symptoms and signs of recurrent ischemic colitis; in one patient, ischemia was endoscopically and histopathologically documented. However, in no patient has catastrophic gut ischemia intervened. Although venous and arterial thrombosis with gangrene of small bowel and colon has been reported with oral contraceptive use (13,14,34,43,48,74,83), it has not occurred in our patient population.

In summary, transient ischemic colitis in young adults manifests with a clinical profile comparable to that in older patients. Women, especially those using oral contraceptives, constitute the high-risk group for colonic ischemia prior to the 5th decade of life. Colonoscopy and mucosal biopsy are effective, complementary methods of securing the diagnosis of segmental ischemic necrosis of the colonic mucosa. In common with transient colonic ischemia unassociated with oral contraceptive use, a favorable long-term outcome is the rule. Reversible ischemic colitis should be considered in the differential diagnosis of acute segmental colitis in young adults. □

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