CLINICAL REVIEW

Superior mesenteric vein thrombosis and oral contraceptives

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Summary

Five cases are reported of superior mesenteric vein thrombosis occurring in women taking oral contraceptives.

The condition is reviewed, and its possible relationship to the drug discussed.

Introduction

Women taking oral contraceptives have an increased risk of developing deep vein thrombosis and pulmonary embolism (Inman & Vessey 1968). The incidence of superficial vein thrombosis is increased (Royal College of General Practitioners, 1967), and idiopathic cerebral vein thrombosis may occur in these patients (Atkinson, Fairburn & Heathfield, 1970). It might be expected therefore that the visceral venous system would also be liable to thrombosis in patients taking oral contraceptives.

Idiopathic superior mesenteric vein thrombosis is an uncommon but well documented condition (Berry & Bougas, 1950; Naitove & Weismann, 1965) that occurs most often in middle-aged or elderly patients. However, four cases have already been reported in young women taking oral contraceptives (Reed & Coon, 1963; Civetta & Kolodny, 1970; Hurwitz *et al.*, 1970) and this paper gives an account of another five such cases; one of these has been seen personally and details of the other four have been obtained with the help of the Committee on Safety of Drugs.

Case reports

Case 1

A housewife aged 40 was admitted to hospital with a 12-hr history of abdominal pain. She had been unwell for several days; the recent pain was severe, colicky, and associated with vomiting. She had been pregnant eight times, and had taken Gynovlar 21 (ethinyloestradiol 50 µg, norethisterone acetate 3 mg) for 5 years. She had also been treated intermittently

with oral iron for anaemia resulting from menorrhagia, but gave no history of other drugs.

On admission she was unwell, with a pulse rate of 120/min and blood pressure 130/80. The abdomen was distended with generalized tenderness but no rigidity, and bowel sounds were absent. Hb, 9.1 g/100 ml; WBC, 25,000/mm³; serum amylase, 111 Somogyi units/100 ml. Plain radiographs of the abdomen showed free fluid, and fluid levels in the small bowel.

At laparotomy blood-stained free fluid was found in the peritoneal cavity. Almost the whole small bowel was dark and thick-walled with an oedematous mesentery. The mesenteric veins contained thrombus which extruded on dissection; the arteries pulsed and bled freely. The affected bowel was excised and end-to-end anastomosis performed leaving about 2½ ft (75 cm) of small intestine. Histological examination of the specimen confirmed venous thrombosis and infarction with normal arteries. No local cause for the thrombosis was apparent.

Postoperative heparin was given, and the patient's initial progress was satisfactory. On the fourth postoperative day, when warfarin had been substituted for heparin, she complained of abdominal pain. The abdomen became distended and tender. Heparin was recommenced, but her condition deteriorated and despite intensive supportive therapy she died 3 days later.

Necropsy. Free blood was found in the peritoneal cavity. The anastomosis had failed to heal, causing peritonitis, and the superior mesenteric vein was solid with thrombus from its smallest tributaries to the portal vein. The splenic vein was similarly thrombosed, and the portal vein showed partial occlusion. Histological examination showed the oldest thrombus to be that in the portal vein, where there was peripheral organization with some fresh clot centrally. The thrombus in the splenic vein appeared the most recent, and that in the superior mesenteric vein intermediate. It was considered that the initial thrombosis

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had been in the portal vein, 1–2 weeks earlier, with subsequent distal spread. No cause was found to account for the thrombosis and in particular no neoplasm was present.

Case 2

A 20-year-old factory worker was admitted to hospital with a history of 3 days' colicky abdominal pain, vomiting and constipation. She had been taking Lyndiol (mestranol 150 µg, lynoestrenol 5 mg) for 6 months; the only other drugs that had been prescribed were antibiotics (ampicillin and tetracycline). The blood pressure was 130/80, and abdominal examination elicited generalized tenderness only. She improved with conservative treatment, but 2 days later vomited 150 ml of blood and was taken to the operating theatre.

At operation. The jejunum was found to be gangrenous, but with the main mesenteric arteries pulsating. Dead bowel was resected and end-to-end anastomosis performed. Paralytic ileus persisted after operation and she died 6 days later with a clinical diagnosis of peritonitis.

Necropsy showed thrombosis of the superior and inferior mesenteric veins and the splenic vein. Thrombus was also found in the deep veins of the leg, and pulmonary emboli were present in the lungs. The mesenteric arteries were patent.

Case 3

A 33-year-old woman had been taking Anovlar (ethinyl oestradiol 50 µg, norethisterone acetate 4 mg) for 9 months. She was admitted to hospital with a 5-day history of abdominal pain and vomiting. Besides oral contraceptives she had been taking salicylates for backache, and potassium perchlorate for control of thyrotoxicosis. The pulse rate was 100 and the blood pressure 130/80; examination of the abdomen elicited right-sided tenderness, which later shifted to the left. The WBC was 6500 mm³. She was treated conservatively but the pain persisted. On the second day after admission she collapsed, and responded to the transfusion of plasma and blood, but the following day collapsed again with a large haematemesis and died.

Necropsy showed thrombus occluding the superior mesenteric, portal and splenic veins with massive small bowel infarction. The main arteries were normal.

Case 4

This 42-year-old woman had a past history of puerperal pulmonary emboli and had been on Lyndiol 2.5 (mestranol 75 µg lynestrenol 2.5 mg) for 4 months. She complained of upper abdominal pain for 10 days, becoming severe and associated with vomiting on the day of admission.

Examination revealed a blood pressure of 130/80, and there was upper abdominal tenderness and guarding. The WBC was 10,100/mm³.

Laparotomy revealed a 3-in (7.5 cm) segment of gangrenous small intestine caused by local superior mesenteric vein thrombosis. The affected segment was resected and after operation warfarin was given. She made a slow but complete recovery.

Case 5

A woman aged 32 presented with a 2-week history of colicky abdominal pain radiating to the back, with associated vomiting. During this time abdominal examination had revealed no abnormal physical signs.

On admission the pain was more severe, and abdominal distension and tenderness were present. The pulse rate was 140/min. She had been taking Orthonovin (mestranol 100 µg, norethisterone 2 mg.) for 18 months. Investigations showed the WBC to be 23,000/mm³.

At laparotomy the same day a 3-ft (90 cm) length of ileum was found to be gangrenous, with thrombosis of the adjacent mesenteric veins. No cause was apparent and the mesenteric arteries appeared normal. The affected segment of intestine was resected; histological examination of this confirmed venous infarction. Low molecular weight dextran was given intravenously daily after operation, but the patient made poor progress and 8 days later a further operation was carried out because of signs of peritonitis. A further 3 ft (90 cm) of ileum distal to the previous anastomosis was gangrenous and required resection. Heparin was given after this operation, and the patient eventually made a full recovery.

Discussion

Superior mesenteric vein thrombosis may be caused by local factors such as trauma, infection, or venous obstruction, or may be associated with hypercoagulable states such as polycythaemia rubra vera and carcinomatosis. The condition was first distinguished from mesenteric arterial obstruction in 1935 (Warren & Eberhard, 1935) and these authors noted a number of cases where no cause, local or general, could be found. This 'idiopathic' superior mesenteric vein thrombosis has since been discussed in detail (Naitove & Weismann, 1965, Trinkle *et al.*, 1969). Its relationship to portal vein thrombosis is unclear, and it has been suggested both that portal vein thrombosis may spread distally to involve the mesenteric veins (Thompson & Sherlock 1964), and also that segmental mesenteric vein thrombosis may spread proximally to involve the portal vein (Mavor, 1966).

Idiopathic superior mesenteric vein thrombosis occurs in all age groups but is most common in the middle-aged and elderly. Men are more often

affected than women. A past history of venous thrombosis occurring elsewhere in the body is common (Naitove & Weismann, 1965; North & Wollenman, 1952) and in forty-three cases collected from the literature such a history is recorded in fifteen (35%). Prodromal symptoms, usually abdominal pain, are common, and the patient presents with symptoms and signs of intestinal obstruction, while late cases have signs of peritonitis. Abdominal physical signs are usually limited to distension and tenderness, and are less than might be expected from the distress of the patient. There are no diagnostic laboratory investigations, but the white cell count is usually raised (often over 20,000/mm³), and peritoneal aspiration may reveal serosanguinous fluid with a normal amylase content. At operation a variable length of small intestine is found to be discoloured and oedematous with a thickened mesentery which hides pulsating arteries. The mesenteric veins-extrude clot when incised.

Treatment is surgical, with wide resection of affected bowel, and the postoperative administration of anticoagulants. The use of anticoagulants is supported by an analysis of forty-three cases reported since 1950 (Table 1). It is of interest to note that of the twenty-five patients who survived after operation, in seven there was a recurrence of superior mesenteric vein thrombosis, but in no case did this occur during treatment with anticoagulants. Late recurrence of superior mesenteric vein thrombosis is known to occur, so that long-term anticoagulant therapy is desirable. The prognosis of the disease is good provided operation is undertaken early enough.

Four cases have been recorded of superior mesenteric vein thrombosis occurring in women taking oral contraceptives (Reed & Coon, 1963; Civetta & Kolodny, 1970; Hurwitz *et al.*, 1970), and five more are here reported. The disease is similar in presentation and clinical course to the 'idiopathic' form, apart from occurring in younger women. The mortality in these cases has been high (56%) and apparently not affected by the use of anticoagulants, although the numbers are small (Table 2). In six cases the contraceptive pill taken was known, and three were of the 'high oestrogen' type containing 100 µg or more of oestrogen preparation. This type

TABLE 1. Outcome of treatment in superior mesenteric vein thrombosis in forty-three cases reported since 1950

Treatment	Survived	Died	Total
Bowel resection, no anticoagulants	10	9*	19
Bowel resection plus anticoagulants	15	0	15
No bowel resection, no anti-coagulants	0	9	9
			43

* Seven of these cases showed necropsy evidence of post-operative extension of thrombosis

TABLE 2. Outcome of treatment in superior mesenteric vein thrombosis in nine cases occurring in women taking oral contraceptives

Treatment	Survived	Died	Total
Bowel resection, no anticoagulants	3	3*	6
Bowel resection plus anticoagulants	1	1	2
No bowel resection, no anti-coagulants	0	1	1
			9

* Two of these cases showed necropsy evidence of post-operative extension of thrombosis

of oral contraceptive is known to be associated with a greater risk of deep vein thrombosis (Inman *et al.*, 1970).

It has been pointed out by Doll & Vessey (1970) that the evaluation of rare side-effects of oral contraceptives is difficult. It requires either prospective trials or large scale retrospective studies. Case reports alone, as presented here, cannot prove a causal relationship. It is of interest that other visceral thromboses have been reported in association with oral contraceptives, for example hepatic vein thrombosis (British Medical Journal, 1971) and superior mesenteric or coeliac artery thrombosis (Brennan Clarke & Macbeth, 1968; Welin & Persson, 1968). Ischaemic colitis has also been described in such patients (Kilpatrick *et al.*, 1968; Ward & Stevenson, 1968; Hurwitz *et al.*, 1970; Cotton & Le Thomas, 1971) but the aetiology of this condition is uncertain. All these conditions are rare, and comparison of the incidence in patients taking oral contraceptives with others is difficult.

At present therefore, it is impossible to prove a causal relationship between oral contraceptives and superior mesenteric vein thrombosis. It is suggested, however, that an accurate record of all drugs taken by a patient is essential, and that the possibility of a visceral venous thrombosis should be considered in any woman who presents with abdominal pain while taking oral contraceptives.

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