Oral contraceptives and myocardial infarction: Report of three cases and review of the literature

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Oral contraceptives and myocardial infarction

Report of three cases and review of the literature

Mohsin Alam, MD, Remigio Garcia, MD, and Ellet H. Drake, MD*

Three cases are presented of young women who had myocardial infarctions possibly due to coronary thrombosis related to oral contraceptive therapy. These patients had none or very few risk factors for coronary artery disease. In two of the patients, selective coronary arteriograms showed normal results on the third and tenth week after the diagnosis was established. The pathogenesis of coronary artery thrombosis in patients receiving oral contraceptives containing estrogen is still controversial, but it appears to be the result of its multifactorial effect on the platelets, coagulation factors, vessel wall, blood pressure, postprandial blood sugar and abnormalities of lipid metabolism.

The association of hormonal contraceptives and myocardial infarction has been reported with increasing frequency in the last twelve years. In recent reports Mann et al. suggested that this increased incidence was probably related to the estrogenic component of oral contraceptives. These authors, as well as the FDA Drug Bulletin, advise against prescribing these preparations for patients who have had thrombotic episodes, ischemic heart disease or other pre-disposing risk factors for coronary disease. We present three additional cases of acute myocardial infarction involving pre-menopausal women who received oral contraceptives. The possible pathogenesis of coronary artery thrombosis and oral contraceptives is discussed with a brief review of the literature.
Case reports

Case 1. B. H., a 22-year-old white female housewife, had been in apparent good health until June 3, 1975 when she was awakened by a retrosternal pressure-like sensation which persisted for over an hour. She was treated in a local hospital where serial electrocardiograms showed an acute inferolateral myocardial infarction (Figure 1). Her serum creatine phosphokinase, serum oxalacetic transaminase, and lactic dehydrogenase were elevated. The patient was a non-smoker and had no history of diabetes or hypertension. She had an uneventful recovery and did not have recurrence of the pains. The patient had been taking Orthonovum 1/50, (which contains 1 mg of Norethindrone and 0.05 mg of Mestranol) for ten months. The patient was referred to our hospital in August, 1975 for coronary angiograms. Her physical examination was completely normal including blood pressure, weight, and cardiovascular system. Significant family history was that her father had suffered three myocardial infarctions.

The laboratory studies were normal including a white blood cell count, hemoglobin, triglycerides, cholesterol, lipoprotein electrophoresis, three-hour glucose tolerance test, antinuclear factor and chest roentgenogram. Cardiac catheterization revealed normal right and left sided pressures. The ventricular contractions were normal. The right and left selective coronary arteriograms were normal (Figure 2).

Case 2. B. S., a 28-year-old black female housewife, was admitted in October, 1973 with a history of severe precordial pressure-like pain. The pain lasted for over an hour, radiated to both shoulders and was accompanied by marked diaphoresis and shortness of breath. The patient had no history of diabetes, hypertension, hyperlipidemia nor previous chest pains. She smoked twenty cigarettes a day and had been taking Ovral (each tablet contains 0.5 mg norgestrel and 0.05 mg of ethinyl estradiol) for four years. The patient’s father had a history of myocardial infarction and is no longer taking the oral contraceptives.

Laboratory tests were all normal including a white blood cell count, hemoglobin, triglycerides, cholesterol, lipoprotein electrophoresis, three-hour post prandial blood sugar. Results of the chest roentgenogram and radioisotope lung scan were negative. The serum creatine phosphokinase, serum oxalacetic transaminase and lactic dehydrogenase determinations showed three to four fold increases from normal values. Serial electrocardiograms were compatible with an anterolateral nontransmural myocardial infarction. Coronary angiograms (Figure 5) were compatible with an anterolateral nontransmural myocardial infarction. The patient had a normal white blood cell count, hemoglobin, serum triglycerides, cholesterol, lipoprotein electrophoresis, venereal disease research laboratory test and a two-hour post prandial blood sugar. Results of the chest roentgenogram and radioisotope lung scan were negative. The serum creatine phosphokinase, serum oxalacetic transaminase and lactic dehydrogenase were all significantly elevated. Serial electrocardiograms showed changes compatible with an acute inferior wall myocardial infarction (Figure 3). The patient had an uneventful hospital course. Cardiac catheterization performed on the seventeenth hospitalization day revealed normal right and left sided pressures except for the left ventricular end-diastolic pressure of 16 mmHg. The left ventriculogram and selective coronary arteriograms were normal (Figure 4).

Case 3. V. P., a 39-year-old white female school teacher with no prior history of chest pain or heart disease, was admitted on April 22, 1971 after three days of intermittent retrosternal and precordial "heaviness". On the day of admission her chest discomfort was more severe and lasted three hours. The chest pain radiated to the left arm and was accompanied by diaphoresis and shortness of breath. There was no history of diabetes, hypertension, hyperlipidemia or cigarette smoking. The patient had been taking Ovral (which contains 0.5 mg of norgestrel and 0.05 mg of ethinyl estradiol) for four years. The patient’s father had a history of myocardial infarction. The physical examination revealed an overweight Caucasian female; blood pressure 120/80, heart size normal with an S4 gallop present.

The patient had a normal white blood cell count, hemoglobin, serum triglycerides, cholesterol, lipoprotein electrophoresis, venereal disease research laboratory test and a two-hour post prandial blood sugar. Results of the chest roentgenogram and radioisotope lung scan were negative. The serum creatine phosphokinase, serum oxalacetic transaminase and lactic dehydrogenase were all significantly elevated. Serial electrocardiograms were compatible with an acute inferior wall myocardial infarction (Figure 3). The patient had an uneventful hospital course. Cardiac catheterization performed on the seventeenth hospitalization day revealed normal right and left sided pressures except for the left ventricular end-diastolic pressure of 16 mmHg. The left ventriculogram and selective coronary arteriograms were normal (Figure 4).

Discussion

In 1963 Boyce et al. were the first to report a case of myocardial infarction in which oral contraceptives were implicated. Since then many similar patients have been reported which are partly summarized in Table I. Certain common features were noted in all the reported cases including ours. All patients were young females; their ages ranged from 22 to 39 years. The majority of these patients received oral contraceptives for periods from five months to eight
Oral contraceptives and myocardial infarction

Fig. 1. Case 1.
Serial electrocardiograms showing evolutionary changes of an acute infero-lateral myocardial infarction.
years. The myocardial infarction was located anteriorly in most patients. The coronary angiograms showed either one of two characteristic findings:

a) a single, smooth lesion located almost exclusively in the proximal left anterior descending coronary artery. No collateral vessels were present and many patients showed akinetic left ventricular wall movements, or

b) normal coronary arteries (as in our two patients studied).

The characteristic single, smooth, proximal lesion and the lack of collateral vessels supports the diagnosis of an acute coronary artery thrombosis as the cause for the myocardial infarction in these cases. The finding of normal coronary arteries in some patients has been attributed to lysis of platelet thrombi or to recanalization of the coronary artery thrombus.

Post mortem examinations in a few cases showed thrombi in the coronary arteries (Table I). According to Mann et al, 83% of the autopsy reports showed a thrombus in

the coronary arteries in women who had died of myocardial infarction and had been using oral contraceptives at the time of death. In comparison, coronary thrombosis was revealed in only 55% of the patients autopsied who had not been taking oral contraceptives, but had died of myocardial infarction. In our cases, we ruled out clinically and by laboratory studies other conditions associated with precocious coronary artery thrombosis such as polycythemia vera, sickle cell anemia, disseminated lupus erythematosus and polyarteritis nodosa.

Estrogens in oral contraceptives have been found associated with an increased incidence of phlebitis and pulmonary embolism. According to pooled data from Sartwell et al,24 and the Royal College of General Practitioners,30 there was 3 to 11 times greater risk of developing deep vein thrombosis and pulmonary embolism in patients who take oral contraceptives. As shown by the collaborative group study,31 oral contraceptives appeared to increase the incidence of thrombotic strokes in young women even in the absence of other risk factors.
Oral contraceptives and myocardial infarction

Serial electrocardiograms showing evolutionary changes of an acute inferior wall myocardial infarction. A was taken on admission and B, C and D were obtained at weekly intervals.
# TABLE I
PERTINENT DATA FROM CASE REPORTS OF 34 PATIENTS WITH MYOCARDIAL INFARCTION AND ORAL CONTRACEPTIVES

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Author</th>
<th>Age</th>
<th>Race</th>
<th>Brand of O.C.</th>
<th>Duration of O.C. Months</th>
<th>Site of M. I.</th>
<th>Risk Factors</th>
<th>Coronary Angiograms &amp; Left Ventriculograms</th>
<th>Autopsy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Boyce et al⁴</td>
<td>32</td>
<td>W</td>
<td>Convid</td>
<td>6</td>
<td>Anterolateral</td>
<td>none</td>
<td>not done</td>
<td>alive</td>
</tr>
<tr>
<td>2.</td>
<td>Hartveit⁵</td>
<td>32</td>
<td>W</td>
<td>Anovlar</td>
<td>5</td>
<td>Posterior wall</td>
<td>none</td>
<td>not done</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Naysmith⁶</td>
<td>33</td>
<td>—</td>
<td>unknown</td>
<td>36</td>
<td>—</td>
<td>—</td>
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<td></td>
</tr>
<tr>
<td>4.</td>
<td>Osborn⁷</td>
<td>34</td>
<td>—</td>
<td>unknown</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Scharf⁸</td>
<td>39</td>
<td>W</td>
<td>Enovid</td>
<td>6</td>
<td>Anterolateral</td>
<td>none</td>
<td>not done</td>
<td>alive</td>
</tr>
<tr>
<td>6.</td>
<td>Stout et al⁹</td>
<td>37</td>
<td>W</td>
<td>unknown</td>
<td>72</td>
<td>Posterior wall</td>
<td>smoker, ↑ cholesterol</td>
<td>not done</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Dalgaardel¹⁰</td>
<td>31</td>
<td>—</td>
<td>Delpregnin</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>—</td>
<td>38</td>
<td>—</td>
<td>Lyndiol</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>—</td>
<td>32</td>
<td>—</td>
<td>Lyndiol</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
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<td>10.</td>
<td>—</td>
<td>32</td>
<td>—</td>
<td>Ovulen</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>—</td>
<td>34</td>
<td>—</td>
<td>Anovlar</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>alive</td>
</tr>
<tr>
<td>12.</td>
<td>Isager et a¹¹</td>
<td>44</td>
<td>—</td>
<td>Lyndiol</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13.</td>
<td>—</td>
<td>41</td>
<td>—</td>
<td>Delpregnin</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>14.</td>
<td>—</td>
<td>40</td>
<td>—</td>
<td>Ovulen</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>15.</td>
<td>Dear et a¹²</td>
<td>27</td>
<td>W</td>
<td>Enovid-E</td>
<td>48</td>
<td>Anteroseptal</td>
<td>none</td>
<td>single proximal LAD occlusion. Akinetic anterior wall</td>
<td>alive</td>
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<tr>
<td>16.</td>
<td>Waxler et a¹³</td>
<td>29</td>
<td>W</td>
<td>C-Quens</td>
<td>8</td>
<td>Posterolateral</td>
<td>smoker, obese</td>
<td>60% LAD lesion. Akinetic posterior wall</td>
<td>alive</td>
</tr>
<tr>
<td>Case</td>
<td>Name</td>
<td>Age</td>
<td>Location</td>
<td>Status</td>
<td>Diagnosis</td>
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<tr>
<td>17.</td>
<td>Glancy et al(^a)</td>
<td>27 W</td>
<td>Oracon</td>
<td>36</td>
<td>Anterior</td>
<td>smoker</td>
<td>LAD lesion akinetic anteroapical wall, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Weiss et al(^a)</td>
<td>35 W</td>
<td>Norlestrin</td>
<td>36</td>
<td>Anterior</td>
<td>none</td>
<td>50% LAD lesion, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Glancy et al(^a)</td>
<td>34 W</td>
<td>unknown</td>
<td>5</td>
<td>Anterior</td>
<td>smoker</td>
<td>normal coronaries hypokinetic anterior wall &amp; dyskinetic apex, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Heefner et al(^a)</td>
<td>36 W</td>
<td>11 day post partum</td>
<td>—</td>
<td>Anterior</td>
<td>smoker</td>
<td>dyskinetic apex &amp; hypokinetic anterior wall, normal coronaries, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Wasdekar et al(^a)</td>
<td>32</td>
<td>unknown</td>
<td>12</td>
<td>Anteroseptal</td>
<td>none</td>
<td>not done, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>Maleki et al(^a)</td>
<td>28 W</td>
<td>unknown</td>
<td>&lt; 12</td>
<td>Anterior</td>
<td>none</td>
<td>not done, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>Maleki et al(^a)</td>
<td>36 W</td>
<td>unknown</td>
<td>&gt; 12</td>
<td>Inferior wall</td>
<td>smoker</td>
<td>normal coronaries hypokinetic apex, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.</td>
<td>Maleki et al(^a)</td>
<td>27 W</td>
<td>C-Quens</td>
<td>36</td>
<td>Anteroseptal</td>
<td>none</td>
<td>not done, * LCA dissecting hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>Maleki et al(^a)</td>
<td>29 W</td>
<td>Ortho-2</td>
<td>15</td>
<td>Anterior</td>
<td>none</td>
<td>80% proximal LAD lesion, alive</td>
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<td></td>
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<td>26.</td>
<td>Maleki et al(^a)</td>
<td>29 W</td>
<td>Ortho-Novum</td>
<td>11</td>
<td>Anterolateral</td>
<td>smoker</td>
<td>proximal LAD occlusion dyskinetic apex, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.</td>
<td>Maleki et al(^a)</td>
<td>38 W</td>
<td>Enovid</td>
<td>&gt; 12</td>
<td>Anterior</td>
<td>none</td>
<td>slight irregularity of LAD, alive</td>
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<td></td>
</tr>
<tr>
<td>28.</td>
<td>Maleki et al(^a)</td>
<td>34 W</td>
<td>unknown</td>
<td>72</td>
<td>Anterior</td>
<td>smoker</td>
<td>proximal 50% LAD lesion akinetic anterolateral &amp; apex. Repeat angiogram normal coronaries, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.</td>
<td>Maleki et al(^a)</td>
<td>38 W</td>
<td>Ovulen</td>
<td>48</td>
<td>Anteroseptal</td>
<td>smoker</td>
<td>not done, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30.</td>
<td>Maleki et al(^a)</td>
<td>27 W</td>
<td>Lyndiol</td>
<td>36</td>
<td>Anteroseptal</td>
<td>smoker</td>
<td>generalized narrowing LAD &amp; circumflex, alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.</td>
<td>Maleki et al(^a)</td>
<td>37 W</td>
<td>Gnovlar</td>
<td>60</td>
<td>Anteroseptal</td>
<td>smoker</td>
<td>not done, alive</td>
<td></td>
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**Present report:**

<table>
<thead>
<tr>
<th>Case</th>
<th>Name</th>
<th>Age</th>
<th>Location</th>
<th>Status</th>
<th>Diagnosis</th>
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<td>Ortho-Novum</td>
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</tr>
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<td>33.</td>
<td>Case 2</td>
<td>28 N</td>
<td>Ovral</td>
<td>3</td>
<td>Inferior wall</td>
</tr>
<tr>
<td>34.</td>
<td>Case 3</td>
<td>39 W</td>
<td>Ovral</td>
<td>48</td>
<td>Anterolateral</td>
</tr>
</tbody>
</table>
In the recent study by Mann et al., there was 2.7 times increased risk for myocardial infarction in patients in the 30 to 39-year-old age group who were taking oral contraceptives. Similarly, there was 5.7 times increased risk for myocardial infarction in women in the 40 to 44-year-old age group who were using oral contraceptives. Furthermore, oral contraceptives appeared to be an independent risk factor for myocardial infarction. The same study showed that the greater the number of risk factors for coronary artery disease (including oral contraceptives, diabetes, hypertension, hyperlipidemia, and cigarette smoking) the higher the risk for developing myocardial infarction. The combined effect of these risk factors appears to be synergistic rather than simply additive.

In another study, Mann et al. found a 2.8 times increased incidence of death from myocardial infarction in women in the 40 to 44-year-old age group who used oral contraceptives as compared to nonusers of the drug in the same age group.

The pathogenesis of coronary thrombosis associated with oral contraceptives is not exactly known. The following studies seem to indicate that many factors are involved:

A) Estrogens have been shown by Caspary et al. and Dugdale et al. to increase platelet adhesiveness. Bolton et al. and Dugdale have shown an increased platelet sensitivity to adenosine diphosphate. Dugdale et al. also showed an increase in platelet number and aggregation with estrogens. These four effects of oral contraceptives (specifically the estrogenic component) on platelets may initiate platelet thrombi in coronary arteries.

B) Estrogens in oral contraceptives have been shown by Pollet et al. to increase factor VII and X activity. This probably makes...
Fig. 5. Case 3.
Serial electrocardiograms revealing evolutionary changes of an acute non-transmural antero-lateral myocardial infarction.
the blood hypercoagulable and initiates venous and coronary artery thrombosis. More recent studies by Handin,^36 Von Kaulla et al^37 and Peterson et al^38 have shown that patients taking oral contraceptives have low anti-thrombin III activity. Anti-thrombin III is a major inhibitor of activated factor X and thrombin. Reduction of anti-thrombin III would make blood hypercoagulable. Peterson et al^38 also showed that estrogen causes increased plasminogen levels. Aronson et al^39 have shown that oral contraceptives increase blood viscosity and hematocrit. Oski et al^40 have reported that oral contraceptives produce increased cell rigidity which may produce stasis in the microcirculation and ultimately thrombosis. This factor may explain thrombosis in small vessels, but not in a major coronary artery. The overall effects of increased blood viscosity, hematocrit, plasminogen, and rigidity of red blood cells and the reduction of anti-thrombin III contribute to make blood hypercoagulable and may initiate coronary artery thrombosis.

C) Mourant et al^41 have shown that patients with blood group A had three times more thrombotic complications with oral contraceptives than patients with blood group O.

D) Estrogens have also been noted to have a direct effect on the blood vessel wall in rabbits. Danforth et al^42 and Irey et al^43 concluded, after autopsy studies on 20 young women, that the use of oral contraceptives possibly caused endothelial and intimal hyperplasia followed by thrombotic occlusion of arteries and veins. Estrogens have also appeared to cause loss of tone of the smooth muscles of the vascular system (Wood^44). In addition, there was a permanent decrease in elasticity of blood vessels. Heefner et al^17 reported a case of acute myocardial infarction due to a hematoma dissecting a coronary artery. This was presumed to be due to direct effect of oral contraceptives on the coronary vessel wall causing cystic medial degeneration and accumulation of mucopolysaccharides in the media.

E) Oral contraceptives have been shown to cause an abnormal rise in post prandial blood sugar (Swerdloff^45). Oral contraceptives also increase serum triglycerides and serum cholesterol level in normal individuals to a slightly higher value. In cases of patients with hyperlipidemia, oral contraceptives may cause excessive elevation of lipids and may even cause pancreatitis. Estrogens also cause elevation of blood pressure in normal individuals; however, in hypertensive patients there is a higher incidence of blood pressure elevation.^45

F) Recently, Astedt and co-workers^46 have found a low content of fibrinolytic activators in the venous vessel wall in 31 women with proven venous thrombosis during oral contraceptive therapy. This fibrinolytic activity seems to be localized to the vasa vasorum. The interesting suggestion was made^47 that the coronary vessels represent ontogenetically the vasa vasorum of the heart and, therefore, are the possible target for suppression of its fibrinolytic activator content by estrogens, increasing its susceptibility to thrombosis.

In summary, it appears that estrogen, by its effects on the platelets, blood clotting factors, blood viscosity, vessel wall, serum, lipids, and blood pressure may play a significant role in initiating acute coronary thrombosis and myocardial infarction.

Pure progestational compounds have been tried by different groups^48 as a possible safer mode of contraception, but the increased pregnancy rate and high frequency of intermenstrual bleeding have restricted their use. Alternative routes and doses of progestagen administration are under investigation, but their effects on the user’s health will require a large and well controlled study.
References


3. FDA Drug Bulletin: Risk of myocardial infarction in users of oral contraceptives. 5:10, July-August, 1975


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