Oral Contraceptives and Hypertension

JAMES W. WOODS

SUMMARY Oral contraceptives result in a mild elevation of blood pressure in most women and overt hypertension in about 5%. Both estrogen and progestogen are responsible for the blood pressure effect, but the mechanism is as yet unknown. The risk of cardiovascular complications is found primarily in women over 35 years of age and in those who smoke. Preparations with an estrogen content of 30 g and a progestogen content of 1 mg or less appear to be safe.

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KEY WORDS • oral contraceptive • estrogen • progestogen • blood pressure • experimental models • mechanisms

It is generally accepted that use of oral contraceptives is etiologically related to a rise in blood pressure. Support for this premise has come from case reports and cross-sectional and longitudinal studies as well as from animal experiments. In this review, answers to the following questions are sought: 1) What is the incidence and severity of the hypertension? 2) Does the hypertension underlie other known complications of oral contraceptives, such as stroke and myocardial infarction? 3) Which component or components of oral contraceptives are responsible and in what dosage? 4) What is the mechanism whereby oral contraceptives elevate blood pressure? 5) Which groups of women are at particular risk? 6) Are there experimental models in which the problem can be studied? 7) What should the general prescribing policy be?

Incidence

Oral contraceptives became generally available in the early 1960s. During this period, their use increased rapidly, and by 1977, it was estimated that about 54 million women were using them worldwide. Since the mid 1970s, publicity regarding complications (primarily the increase in the risk of cardiovascular disease) has undoubtedly been responsible for the decline in their use in the United States. Analysis of these complications is made difficult by the large number of publications involving small numbers of subjects, the absence of suitable controls in many reports, the varying composition of preparations in past and present use, and the fact that some combinations of estrogen and progestogen act synergistically and others antagonistically. Consequently, differing conclusions abound in the literature on this subject. Here, an attempt will be made at a synthesis and overview of major findings and not a critique of the methodological strengths and weaknesses of the various studies cited.

By 1963, case reports of thromboembolic disease in women using oral contraceptives were numerous, and by 1967, the first reports suggesting an association between oral contraceptives and hypertension appeared. The incidence in early studies varied widely. For example, Tyson found that 15.5% of 45 women taking oral contraceptives developed an elevated blood pressure and Saruta and colleagues found elevated pressure in 18% of 56 women. In the prospective study of Weir and co-workers, 83 users of oral contraceptives were observed and compared with a control group that used mechanical methods of birth control over a 3-year period. Increases were found in mean systolic and diastolic blood pressures of 9.2 and 5.0 mm Hg, respectively. After an additional year, in a smaller group, the mean rise in systolic pressure was 14.2 mm Hg and in diastolic pressure, 8.5 mm Hg. Blood pressure returned to pretreatment levels within 3 months after hormonal therapy was stopped. Clezy and co-workers in Australia, using a blood pressure of greater than 150/90 mm Hg as the definition of hypertension, observed that 4% of 76 women developed hypertension.

Three major cohort studies of women using oral contraceptives began in 1968. In the two British studies, the Royal College of General Practitioners (RCGP) Oral Contraception Study and the Oxford University/Family Planning Association Study, the investigators are still collecting and analyzing data. A United States study, the Walnut Creek Contraceptive Drug Study, ended in 1977, and the final report was published in 1981. The latter study, based on data from 11,672 women, demonstrated a pressure elevation of 5
to 6 mm Hg systolic and 1 to 2 mm Hg diastolic that was attributed to oral contraceptive use. There was a sixfold increase in the risk of overt hypertension. The even larger RCGP Study involving 46,000 women found that users were 2 to 2.5 times more likely to develop hypertension than nonusers. The Stanford Three-Community Study, involving 986 women, found that the average systolic blood pressure was 7.2 mm Hg higher in white users than in nonusers, but among Mexican-American women, average systolic blood pressure was 19.9 mm Hg higher, and average diastolic pressure was 9.4 mm Hg higher. Finally, Blumenstein and co-workers have presented data on 2676 southeastern black women and found no difference in mean blood pressure between control and oral contraceptive groups over a 6- to 24-month period. However, these women were young, with a mean age of 23.2 years. The risk of hypertension that is attributable to oral contraceptives has been observed to increase with age, becoming substantial only in women about 35 years of age or older. However, these women were young, with a mean age of 23.2 years. The risk of hypertension that is attributable to oral contraceptives has been observed to increase with age, becoming substantial only in women about 35 years of age or older.9 Khaw and Peart in a survey of 461 women found no difference between white and black women and a 5-mm higher mean blood pressure in users than in nonusers.

In summary, it is clear that oral contraceptives elevate blood pressure in most women, and this elevation is small on the average. However, existing hypertension may be worsened, and malignant hypertension may be produced rarely. In a population in which a larger proportion of healthy women are using oral contraceptives, a small shift in the distribution of a risk factor may have a great impact on the community’s overall burden of disease, and there is no doubt that smoking is responsible for the increased risk of stroke and myocardial infarction in oral contraceptive users. In regard to mortality, the RCGP Study found that the death rate from circulatory disease in women who had used oral contraceptives was nearly five times that of controls who had never used them. This risk increased with age and was greater in smokers than in nonsmokers.

Role of Estrogen Versus Progestogen in Cardiovascular Complications

Until 1980, the published epidemiological data concerning untoward effects of female hormones made little mention of progestogens. The evidence for a dose-response effect of estrogens has been a strong argument for a causal effect of this agent. In addition, a multiplicity of progestogen preparations in oral contraceptives resulted in a paucity of epidemiological research directed to this component. Recent studies provide evidence of the importance of estrogens in the risk of both overt and subclinical thromboembolic disease. Further, an estrogen content of 50 to 80 μg is only one third to one half as likely to produce this as is a content of 100 to 150 μg. The mechanism would appear to be endothelial proliferation, decreased venous blood flow, and increased coagulability. The risk of myocardial infarction and stroke appears to be related to both estrogen and progestogen content. The risk is primarily concentrated among older women and women with other risk factors, such as cigarette smoking and hypertension. It is of interest and of probable importance that estrogens increase high density lipoprotein cholesterol, while progestogens decrease it. Estrogens have until recently been thought to be responsible for the increased blood pressure associated with oral contraceptives. Recent evidence implicates progestogens as well.

The effect of oral contraceptives of varying composition on blood pressure is shown in Table 1. The study of Spellacy and Birk was prospective and involved 415 normotensive women observed over a 6- to 12-month period. The development of diastolic hypertension while taking oral contraceptives was significantly higher if the women had hypertension in a pregnancy previously. Weir’s subjects were 30 women with persistent hypertension induced by high-dose combinations containing 50 μg estrogen and 1 to 4 mg progestogen. A marked significant fall in blood pressure had occurred after 6 months with either a low-dose preparation or progestogen alone. However, pressure did not fully return to pre–oral contraceptive levels. In the RCGP Study women on a fixed dose of 50 μg ethinyl estradiol and three different doses of progestogen, there was a positive correlation between the progestogen and hypertension. Khaw and Peart carried out a cross-sectional study on 461 women and found that those taking oral contraceptives had significantly higher mean systolic and diastolic blood pressures than those using nonhormonal contraception. There appeared to be a dose-response relation of blood pressure to the progestogen component of two oral contraceptives with an identical 30-μg ethinyl estradiol component. There was a significant correlation of blood pressure with duration of current use of oral contraceptives. In women taking oral contraceptives, those who had either a history of hypertension in pregnancy or a family history of hypertension had significantly higher mean blood pressures than those who did not. In the study by Briggs and Briggs, there was no significant change in blood pressure in either the control (IUD) or 30-μg estrogen group. In contrast, the 50-μg estrogen group showed a gradual increase over the initial 3-year period.

Oral Contraceptives and Elevated Blood Pressure

The mechanism by which oral contraceptives elevate blood pressure has not been identified. The renin-angiotensin-aldosterone system has been the principal suspect since estrogen administration stimulates the hepatic synthesis of plasma renin substrate, which is the rate-limiting step of the renin reaction under physiological conditions. Plasma renin activity and angiotensin II (Ang II) have been elevated in some studies and not in others. Plasma renin concentration is usually reduced possibly because of feedback suppression by...
Table 1. Effect of Oral Contraceptives of Varying Composition on Blood Pressure

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Subjects</th>
<th>Estrogen (dose)</th>
<th>Progestogen (dose)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spellacy and Birk</td>
<td>30 (Ctrls)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>123</td>
<td>100 µg</td>
<td>1 mg</td>
<td>5*</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>80 µg</td>
<td>0</td>
<td>6*</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>50 µg</td>
<td>0</td>
<td>7*</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.25 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>0</td>
<td>400 mg i.m.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>0</td>
<td>0.075 mg</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>0</td>
<td>0.25 mg</td>
<td>0</td>
</tr>
<tr>
<td>Weir</td>
<td>14 (170/111 mm Hg)</td>
<td>30 µg</td>
<td>150–250 µg</td>
<td>152/93 mm Hg</td>
</tr>
<tr>
<td></td>
<td>16 (174/113 mm Hg)</td>
<td>0</td>
<td>350 µg</td>
<td>144/95 mm Hg</td>
</tr>
<tr>
<td>RCGP-OC Study</td>
<td>89</td>
<td>50 µg</td>
<td>1 mg</td>
<td>8.19*</td>
</tr>
<tr>
<td></td>
<td>170</td>
<td>50 µg</td>
<td>3 mg</td>
<td>12.30*</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>50 µg</td>
<td>4 mg</td>
<td>13.88</td>
</tr>
<tr>
<td>Khaw and Peart</td>
<td>176 (Ctrls)</td>
<td>0</td>
<td>0</td>
<td>mean sys/dias</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>30 µg</td>
<td>150 µg</td>
<td>109.3/70.1 mm Hg</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>30 µg</td>
<td>250 µg</td>
<td>111.4/71.1 mm Hg</td>
</tr>
<tr>
<td></td>
<td>53 (Ctrls)</td>
<td>0</td>
<td>0</td>
<td>Δ mean sys/dias</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>50 µg</td>
<td>1 mg</td>
<td>+1/+2</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>30 µg</td>
<td>150 µg</td>
<td>+12/+8</td>
</tr>
</tbody>
</table>

*% with blood pressure > 140/90 mm Hg.
Hypertension rate per 1000 women years.
P<0.005.
P<0.05.

Angiotensin. Estrogens clearly do not stimulate the synthesis and release of renin by the kidney. Although all women who take a sufficient quantity of estrogen have increases in substrate levels, only a small percentage develop hypertension. There is also no difference in the absolute circulating levels of renin substrate or Ang II in women with oral contraceptive-induced hypertension and normotensive women receiving equal doses of the hormones. Additional factors are obviously necessary for the development of hypertension. Further evidence against the possibility of the renin-angiotensin system playing an etiologic role in oral contraceptive-induced hypertension involves studies in both women and rats in which infusion of the Ang II antagonist [sarcosine 1, isoleucine 8] failed to alter blood pressure.

Since estrogens (but not progestogens) have a weak positive effect on fluid volume, this action has also been investigated as a possible cause of blood pressure elevation. The effect has been shown not to be produced by aldosterone, and the effects on renal hemodynamics are minimal. There are large differences in response to estrogens from species to species. Measurements of total body sodium and potassium in a group of women who developed hypertension while taking oral contraceptives were compared with similar measurements in age-matched women without hypertension and revealed no differences, and the values were normal in both groups. Aitken et al. studied the effects of both long-term mestranol and placebo in 175 oophorectomized women, and they found evidence to support the hypothesis that estrogen-induced fluid retention is the result of primary water retention with secondary redistribution of body sodium.

Red cell sodium-lithium countertransport is increased in patients with essential hypertension, in pregnancy, and in women on oral contraceptive therapy. Weder has recently reported that the rate of sodium reabsorption by the proximal renal tubule as measured by renal lithium clearance is increased in patients with essential hypertension who have increased red cell sodium-lithium countertransport. He postulates that red cell countertransport is a marker of the renal abnormality. By analogy, oral contraceptives might produce this renal abnormality, and this deserves further study.

Although an unlikely general cause of hypertension secondary to oral contraceptives, intrarenal vascular lesions have been described in small numbers of patients receiving oral contraceptives. Boyd et al. described nine patients who developed reversible hypertension and evidence of impaired renal function while on oral contraceptives. Renal angiograms and biopsies revealed microthrombosis involving glomerular capillaries or intrarenal arterioles and microangiopathic hemolytic anemia. Withdrawal of oral contraceptives was followed by clinical improvement.

Oral Contraceptive-Induced Hypertension in the Rat

Since 1940, many investigators have been able to either induce hypertension in normal rats or to cause aggravation of hypertension in such experimental models as the spontaneously hypertensive rats, Dahl.
salt-sensitive rats, or those with hypertension produced by deoxycorticosterone-salt. A few investigators have had negative results, but these experiments usually involved short-term administration of the hormones. Noteworthy are the studies of Fregley,26 Stubbs and co-workers,27 and Fowler and colleagues.28 The hormones were administered in the chow for 5 to 6 months, and blood pressure was measured by carotid cannulation in addition to the tail-cuff method. The dose of oral contraceptives given to rats to induce hypertension was three to four times the dose ingested daily by humans on a weight basis—a large but not immense dose. Similarities exist between oral contraceptive–induced hypertension in humans and the hypertension developed in this rat model. The hypertension is usually mild in humans and in these rats, with mean arterial pressures increasing by only 14 to 28 mm Hg. Furthermore, in Fowler’s rats with oral contraceptive–induced hypertension, plasma renin substrate was markedly elevated, with plasma renin activity and plasma renin content values that were not greatly altered.21 In this study, it was apparent that the estrogenic component was the steroid responsible for producing hypertension. The infusion of [Sar^1,Ile^8]Ang II in doses sufficient to block the pressor response to infused Ang II failed to lower the arterial pressure in the hypertensive rats treated with mestranol or in those treated with mestranol plus norethynodrel; this is strong evidence that the hypertension was not simply due to the effect of elevated plasma levels of Ang II on vascular smooth muscle cells. These results are in contrast to earlier ones of Stubbs,27 who in the same laboratory did obtain a fall in pressure with another Ang II antagonist, [Sar^1,Ala^4]Ang II. Their results may have been due to pentobarbital, an anesthetic agent known to increase renin release.

Prescribing Policy

In addition to being a highly effective method of preventing unwanted pregnancy, oral contraceptives are now recognized as having multiple health benefits. However, weighing against these benefits are the risks of oral contraceptive use, primarily those of cardiovascular origin. Deaths from cardiovascular disease in young healthy women who take oral contraceptives are very few, whereas deaths are largely concentrated in older women, particularly those who smoke. The data favor use of preparations with low estrogen-progestogen content, although this content was not established. Oral contraceptives should be prescribed with caution in women who are obviously hypertensive or in women with a history of hypertension during pregnancy, with a strong family history of hypertension, or with a family history of early coronary artery disease. Blood pressure and serum lipids should be followed and regular surveillance should be insisted on. The availability of safe oral contraceptives is particularly important because of the recent withdrawal from the market of the most commonly used IUD. This was brought about when the cost of defending the device in personal injury cases became prohibitive.

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