Editorial:
Possible Hazards of Oral Contraceptive Use

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ORAL CONTRACEPTIVES have been reported to affect all serum lipids, but their effect on the triglycerides and VLDL is most consistent and striking.\(^1\)\(^2\) Though changed, the lipids generally remain within usual limits, but occasionally, a pronounced hypertriglyceridemia occurs.\(^2\)\(^3\) These extreme responses (even, on occasion, with hyperlipemic crises and pancreatitis) appear to be most likely in women predisposed by diabetes or preexisting type 4 VLDL abnormality. This oral contraceptive-induced hypertriglyceridemia appears to result from enhanced VLDL production stimulated by estrogen.\(^4\)\(^5\) However, the plasma triglycerides rise higher than expected from the size of the VLDL cholesterol increase, and there is also an increased triglyceride turnover rate.\(^6\)\(^7\)\(^8\) There may also be a quantitative alteration of the VLDL with a decreased APO-C2 lipoprotein content. In contrast to estrogen, progestagens tend to increase the rate of clearance of triglyceride.\(^9\)\(^10\)

In considering the public health implications of the lipid aberrations which accompany the use of oral contraceptives, it is important to recognize that pregnancy is also accompanied by an increased triglyceride level;\(^11\)\(^12\) a rise in serum total cholesterol is also common. This appears not to have affected the vulnerability of women to atherosclerotic vascular disease, since the incidence of such disease is unrelated to parity. Furthermore, there is no clearly demonstrated independent contribution of triglycerides per se to atherogenesis in either sex.\(^9\)\(^12\) Nevertheless, marked rises in triglycerides or VLDL on oral contraceptive administration cannot be viewed with equanimity.

More important, oral contraceptives may also raise the serum total cholesterol and LDL, particularly in young women. This has not been as consistently demonstrated, and does not occur to the same degree as for triglyceride, but these lipids do appear to make a significant independent contribution to coronary heart disease risk.\(^12\) Oral contraceptives that contain estrogen may secondarily raise the serum total cholesterol by elevating the VLDL and the HDL cholesterol containing lipoprotein fractions.\(^12\) There is no reason to believe that this type of hypercholesterolemia is atherogenic. However, the changes in HDL reported are still rather inconsistent, and even though HDL cholesterol appears to be protective, the effect of oral contraceptive-induced changes in HDL on atherogenesis is still only speculative.

Type 5 hyperlipoproteinemia may be induced by oral contraceptive use in women with type 4 abnormality. This may also occur with ethanol intake in oral contraceptive users.\(^13\) On the other hand, type 3 dyslipoproteinemia may be improved by estrogen-containing oral contraceptives.\(^5\)

These effects must be put into perspective, since oral contraceptives are now the most preferred and the most effective method of contraception. No contraceptives in use, including oral contraceptives, have an associated death rate as high as that for pregnancy itself or for abortions for unwanted pregnancies.

However, oral contraceptives worsen the major atherogenic cardiovascular risk factors to some degree in all women which, while they may remain within normal limits, are uniformly shifted upward, raising the mean level of the whole distribution of cardiovascular risk factors in a substantial proportion of the female population.\(^14\)\(^15\) Some susceptible women suffer marked aberrations and develop severe hypertension, hypertriglyceridemia and overt diabetes. All these atherogenic effects could eventually have serious consequences beyond the childbearing years. Left uncontrolled, these effects, plus the effects on blood clotting and on the vessel itself, threaten to eradicate the normal female advantage over men as regards cardiovascular mortality.

During the childbearing years there is a demonstrated small but real escalation of risk of thromboembolic events. While the relative risk is large, the absolute risk is small. These acute effects of oral contraceptive use do not appear to be an atherosclerotic phenomenon, but rather a consequence of effects on various elements of blood clotting, fibrinolysis, and platelet adhesiveness. Also, histochemical and pathological anatomical changes in blood vessels have been noted of an inflammatory, and degenerative nature.\(^16\)\(^17\)\(^18\) These vascular and clotting aberrations may also contribute to an accelerated pace of atherogenesis to become clinically manifest beyond the reproductive years. Pooled serum from oral contraceptive users has also been found to promote proliferation of arterial smooth muscle cells in culture, a phenomenon which is a prominent feature of atherogenesis.

Prospective studies now corroborate retrospective reports that show a substantially increased risk of thromboembolic disease during the reproductive years.\(^19\)\(^20\)\(^21\) Post-surgical complications are also increased. In heavy smokers over age 40 years, thromboembolic risk exceeds that associated with childbirth threefold, but also when one or more cardiovascular risk factors compounds the risk of a car-
diovascular catastrophe. More information is needed on the pathogenesis of the oral contraceptive-induced thromboembolic sequelae in the childbearing age that appear to be related to the estrogen content of the oral contraceptives.

The full impact of oral contraceptives on cardiovascular risk factors may not be fully appreciated from the short duration studies done so far. Studies indicate that 5% of women who use oral contraceptives will develop clinical hypertension within 5 years, an incidence 2.6 times greater than that of women who do not use oral contraceptives. They also indicate that the incidence may increase to 15% after 5 years of use.

The preceding article of Hennekens et al. in this issue of Circulation suggests that this may not be the case for triglyceride, but data is sparse on that point for LDL-cholesterol and HDL-cholesterol. Also, while the lipid and blood pressure aberrations produced appear reversible on discontinuing the therapy, it is not clear that atherogenic effects over 3 decades of oral contraceptive use are as reversible.

More specific guidelines are needed for monitoring women on oral contraceptives for worsening of their atherogenic traits and changes in blood coagulation. Indications and contraindications for oral contraceptive use must be better defined in relation to their thromboembolic hazards. Oral contraceptive use would appear imprudent for women with a history of hypertension, impaired glucose tolerance or lipid aberrations, in themselves or close relatives. Care is also needed for those undergoing prolonged immobilization and surgery.

Thus far, trends in cardiovascular mortality in women show nothing alarming. In fact, mortality has been declining since 1968 despite widespread use of oral contraceptives. Nevertheless, potentially dangerous biochemical and physiologic changes accompany their use and it may be too soon to know the full cost. We must learn to use these drugs more wisely and keep their users under closer surveillance. Efforts should continue to produce safer effective oral contraceptives.

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