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Oral Contraceptives and Plasma Lipoprotein Metabolism

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Oral Contraceptives and Plasma Lipoprotein Metabolism

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I. Introduction

While the relationship of oral contraceptive (OC) use to cardiovascular disease (CVD) is likely to be multifactorial, effects on plasma lipid and lipoprotein metabolism are of potential importance (1,2). Commonly used OC preparations result in elevations in plasma triglycerides (TG), very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL), and reductions in high-density lipoproteins (HDL), particularly the HDL_2 subclass. In this chapter, hormonally-mediated lipid and lipoprotein metabolic alterations and effects of commonly used combination OC preparations are described within the general context of lipoprotein metabolism and the relationship of lipoprotein parameters to CVD.

II. Plasma Lipoprotein Metabolism and Relationship to Cardiovascular Disease

Exogenously and endogenously derived lipids are assimilated within lipoprotein complexes for transport between tissues. The origins and metabolic fate of lipoprotein-borne lipids depend on the identity of the lipoprotein carrier. Individual lipids may reside on several lipoprotein species while in circulation, either as a result of transfer between lipoproteins, or by remaining associated with a particle which undergoes transition from one species to another.

A. Apolipoprotein B-containing Lipoproteins

Dietary lipids are combined with the structural protein apolipoprotein (apo) B-48 in the intestines to form large complexes known as chylomicrons. Following lipolysis and uptake of chylomicron triglyceride by peripheral tissues, cholesterol-enriched remnants are taken up by the liver via receptor-mediated processes. A portion of the lipids are metabolized in the liver and the remainder are repackaged into VLDL for delivery to cells of the periphery. VLDL comprise a heterogenous array of particles containing variable amounts of lipids including endogenously synthesized TG and cholesterol and phospholipids, a higher molecular weight form

of apo B (apo B-100) which serves as a cell surface receptor ligand, and several smaller proteins (apos E and C) with critical metabolic properties. Surface lipids are liberated from VLDL by the action of lipoprotein lipase (LPL) in the capillary endothelium for uptake by tissues and other lipoproteins (e.g., HDL), and in the process are converted to TG-depleted remnants which may be taken up by the liver for further processing. Larger VLDL and VLDL-derived remnant particles are cleared more efficiently than smaller VLDL for reasons which are still incompletely understood. Under conditions of inefficient clearance with increased plasma residence time, remnant particles undergo further TG depletion and accumulate cholesterol transferred from HDL yielding VLDL remnants and cholesterol-enriched intermediate-density lipoproteins (IDL). IDL are further degraded to LDL, which contain the major portion of cholesterol found in human plasma. LDL particles are taken up by hepatic apo B-100 receptors. However, when this system is saturated, excess LDL and IDL are removed more slowly and accumulate in plasma.

High circulating levels of apo B-containing lipoproteins are associated with increased risk of CVD, and considerable evidence indicates that these lipoprotein species, particularly LDL, participate directly in the atherogenic process. Pathophysiologic chemical modifications, most notably oxidative modifications, appear to be critical in predisposing lipoproteins to participate in atherogenic processes. A variety of alterations in lipoprotein physicochemical properties may affect susceptibility to oxidative changes, and consequently may alter disease risk. Like VLDL, LDL consist of a heterogenous group of particles differing in physicochemical, metabolic, and atherogenic properties. Smaller LDL subspecies appear to be more susceptible to oxidative modifications (3,4), and this may explain the increased risk associated with lipoprotein profiles enriched in such particles (5).

B. High Density Lipoproteins

In contrast to apo B-containing lipoproteins, HDL are inversely associated with CVD and these lipoproteins are suggested to be antiatherogenic. HDL are formed from proteins, primarily apos A-I and A-II, that are synthesized by liver and intestines and combine with lipids removed from other lipoproteins and from tissues. TG-rich lipoproteins (chylomicrons and VLDL) contribute the bulk of HDL lipid mass. Cholesterol accumulation is facilitated by HDL-associated lecithin:cholesterol acyl transferase (LCAT) activity, which catalyzes the formation of cholesteryl esters and the subsequent displacement of these molecules to the hydrophobic lipoprotein core. Continued cholesterol uptake promotes the assimilation of additional apo A-I molecules when particles attain certain critical masses, resulting in the formation of a series of discrete particles of increasing size known as HDL_3, HDL_{2a}, and HDL_{2b}.

Circulating HDL and HDL subclass concentrations are determined by the rates of synthesis and catabolism of the constituent apolipoproteins, as well as the efficiency of metabolism of TG-rich lipoproteins. LPL activity liberates lipids for uptake by HDL and thus is associated with plasma HDL concentrations. In contrast, the activity of hepatic lipase (HL), which degrades HDL lipid components, is inversely associated with HDL and HDL_2 concentrations in plasma.

The apparent antiatherogenicity of HDL is thought to arise predominantly from the role of these lipoproteins in "reverse cholesterol transport", a cycle involving tissue cholesterol uptake by HDL and its subsequent transfer to the liver, either directly or following transfer to VLDL or LDL. Through this process, HDL play a critical role in cellular cholesterol homeostasis and thereby may be capable of altering the course of atherosclerotic lesion growth. Plasma levels of apo A-I and HDL_2, particularly HDL_{2b} which possesses the greatest cholesterol carrying capacity, are suggested to provide an index of the efficiency of reverse cholesterol transport (6).

Recent reports have suggested that HDL also may protect against atherogenic oxidative changes (7,8), and this property may be antiatherogenic. The nature of the HDL antioxidant effects are currently unknown but represents an area of extensive research interest.

In addition to a direct antiatherogenic role, levels of HDL and HDL subclasses may serve as surrogate measures of other critical metabolic factors influencing CVD risk. HDL levels are related to the efficiency of TG-rich lipoprotein metabolism, and therefore may reflect the extent to which these lipoproteins are available to promote disease. Although the atherogenicity of TG-rich lipoproteins has not been established, these lipoproteins have been shown to perturb endothelial cell metabolism and promote macrophage lipid accumulation (see ref. 9). Low HDL levels are noted in individuals exhibiting an LDL profile characterized by a predominance of small, dense particles along with elevated TG and IDL levels, and thus may serve as a marker of an atherogenic lipoprotein phenotype (5).

III. Effects of Oral Contraceptive Hormonal Components on Lipoprotein Metabolism

A. Estrogens

Estrogen administration results in numerous alterations in the metabolism of apo B-containing lipoproteins. Elevations in circulating TG and VLDL concentrations occur as a result of increased rates of hepatic synthesis of TG and apo B-100. In postmenopausal women receiving micronized estradiol, larger VLDL particles appear to be increased preferentially, and most are cleared directly from plasma, with smaller amounts converted to small VLDL and LDL (10). Estrogen also affects LDL concentrations, albeit less consistently, and the nature of such effects appear to depend on the underlying hormonal and physiological environment. Whereas contraceptive estrogens may lead to elevations in LDL concentrations in

premenopausal women, postmenopausal estrogen replacement usually results in LDL-cholesterol lowering (11).

Elevations in HDL occur consistently with estrogen administration and appear to be mediated by increased synthesis of HDL apolipoproteins, primarily apo A-I (12), as well as suppression of HL activity in post-heparin plasma. The latter may be especially important in elevating HDL_2 (13,14). Increased HDL_2 concentrations also may result from decreased cholesterol transfer to remnant particles and LDL, which serve as acceptors of HDL lipids.

B. Progestins

Numerous progestins have been developed for contraceptive purposes including derivatives of progesterone (e.g., medroxyprogesterone) and androgenic nortestosterone (e.g., norgestrel). The more androgenic progestins in OC bring about reductions in plasma concentrations of TG, VLDL, HDL and HDL_2, and elevations in plasma LDL levels. Mechanisms underlying progestin effects on apo B-containing lipoproteins are not understood. HDL lowering effects are attributed, at least in part, to increased HL activity leading to accelerated HDL metabolism and clearance (14). Metabolic studies have shown that changes in HL activity and HDL concentrations are highly correlated with progestin androgenicity which, according to such responses, varies over at least a ten to twenty-fold range (15).

Progestin-induced elevations in VLDL and reductions in HDL concentrations also may be influenced by alterations in carbohydrate metabolism and insulin action. Progestins have been shown to promote glucose intolerance and insulin resistance (16), and as with lipoprotein changes, the extent of such effects are a function of the progestin dose and androgenicity.

III. Effects of Combination Oral Contraceptives on Plasma Lipoproteins

OC regimens in common use today consist of fixed doses (35-50 μg/day) of estrogen (mestranol or ethinyl estradiol [EE]) in combination with fixed (monophasic) or variable doses (multiphasic) of progestin. The nature and extent of OC-mediated lipid and lipoprotein changes vary considerably depending on the relative contents of estrogen and progestin, and the androgenicity of the progestin component.

In a study involving the Lipid Research Clinics population, Wahl et al (17) compared lipoprotein levels in women receiving OC preparations with varying hormonal components and doses (see Table I). Three combination steroids were studied: Ortho-Novum (mestranol and norethindrone [NE]), Norlestrin (ethinyl estradiol [EE] and norethindrone acetate [NEA]), and Ovral (EE and *dl*-norgestrel [NG]). Plasma TG concentrations and VLDL were increased in women using all three preparations and LDL concentrations were increased in women using Norlestrin or Ovral as compared with nonusers. HDL concentrations were slightly increased with Ortho-Novum, but were considerably decreased with Ovral. Thus, the progestins exhibited minimal effects in opposing estrogen-induced elevations in TG-rich lipoproteins, but attenuated estrogen-induced elevations in HDL, with the greatest HDL lowering occurring in response to the more androgenic progestin (i.e, NG).

{INSERT TABLE 1 ABOUT HERE.}

In the Walnut Creek Contraceptive Drug Study (18) lipoprotein profiles were examined in users of combination agents containing estrogen and NE as categorized by dose (see Table II). TG were elevated at all doses. While the lowest dose formulations had no impact on LDL concentrations, OCs containing lower dose estrogens with higher doses of NE were associated with elevated LDL. Higher dose

estrogen had no effect on LDL concentrations unless combined with higher dose progestins. Thus, the LDL response was governed by the progestin component such that elevated LDL concentrations were observed with high dose progestins in combination with any estrogen dose. HDL concentrations were reduced in women using low dose estrogens in combination with higher dose progestins, and elevated in women using higher dose estrogen when combined with lower but not higher dose progestins.

{INSERT TABLE 2 ABOUT HERE}

Godsland et al (19,20) examined lipoprotein levels in a cross-sectional sample of women who took one of seven combination OC preparations containing various doses of the progestins NE, levonorgestrel (*d*-norgestrel, LNG), or desogestrel (DG). Levels of apos B, A-I and A-II were generally increased in response to combination OCs. Both low and high doses of LNG were associated with decreased HDL and HDL_2 levels, especially when present in monophasic preparations, but effects were reduced at lower doses. The most favorable profiles were observed in users of OC formulations containing NE, particularly at lower doses, and DG, which were associated with reduced LDL and increased HDL concentrations.

Similar results have been reported in longitudinal studies. Lipson et al (21) examined the effects of three high-dose OCs containing the progestins ED, NEA, and NG in a randomized one-year trial involving 150 women (50 women per group) (see Table III). TG elevations were observed in all groups and LDL were elevated in groups using ED and NG. HDL were significantly reduced with NG, and effects occurred almost exclusively in the HDL_2 fraction. A nonsignificant decrease in apo A-I concentrations also was noted with this preparation, in contrast to those containing NEA and ED, which produced elevations in plasma apo A-I. Apo A-II

concentrations were elevated with all three preparations. Thus, as predicted from cross-sectional studies, the most deleterious lipoprotein changes occurred with the OC preparation containing the more androgenic progestin (i.e., NG).

{INSERT TABLE 3 ABOUT HERE}

The effects of progestins ED, NE and LNG in combination with lower dose estrogen (30-35 μg) were monitored in a 7-week randomized clinical trial involving 63 to 70 women per treatment group (22). The OC preparation containing LNG produced a significant decrease in HDL and a nonsignificant decrease in apo A-I. Plasma apo A-I concentrations were elevated by both ED and NE, and the former progestin produced a slight increase in HDL. Thus, the estrogenic and androgenic effects of the various OC hormonal components, although blunted, are still observed with lower dose OC preparations. In another study, Krauss et al (23) reported that lower dose OC agents containing NE and NG also produced differential effects on HDL subfractions, with NE-related increases in HDL_3 and HDL_{2b}, and NG-related reductions in HDL_{2b}.

In general, less marked lipoprotein changes are observed with triphasic as compared with monophasic preparations containing similar progestins components (20,24), although the nature and extent of lipoprotein responses vary across the treatment cycle. Lussier-Cacan et al (24) noted temporary but significant reductions in plasma total- and LDL-cholesterol during the first week of the cycle corresponding to the lowest progestin (NE) dose, but levels returned to baseline over the ensuing three weeks. These investigators also showed that following twelve therapeutic cycles, OC-mediated lipoprotein alterations essentially returned to baseline values within one posttreatment cycle.

Less deleterious lipoprotein alterations have been observed in response to the newer nortestosterone derivatives with minimal androgenicity including norgestimate (25) and DG. Several studies have shown that, with the exception of elevations in TG concentrations in monophasic preparations, OCs containing DG as the progestin component do not adversely affect plasma lipoprotein levels (26,27). Fioretti et al (28) observed increased HDL cholesterol concentrations, an increased ratio of HDL to LDL cholesterol, and increased concentrations of apos A-I and A-II with OCs containing EE and DG, while LDL cholesterol concentrations remained stable. Ylikorkala et al (29) similarly reported that treatment with a DG-containing OC increased concentrations of HDL and HDL2. While increased TG concentrations were noted with monophasic DG-containing preparations (27,28), the effects on HDL-cholesterol levels are likely to override any deleterious effects attributable to increased TG.

Despite the lack of adverse effects of DG on lipoprotein levels, this progestin (and LG) has been shown to alter LDL physicochemical properties. Kauppinen-Makelin et al (27) reported increased LDL triglyceride levels in users of OCs containing DG and LG. These changes together with previous reports that OCs result in increased LDL protein content and density (see ref. 27) and our observation that OC-induced elevations in LDL mass primarily involve smaller, denser protein-enriched LDL subspecies (30) suggest that combination OC use may result in the formation of more atherogenic lipoprotein subspecies independent of changes in absolute lipoprotein levels.

V. Summary and Conclusions

While current evidence has not established the extent to which OC-induced lipid and lipoprotein changes may influence CVD risk, the potential for atherogenic lipoprotein changes should be considered in evaluating the metabolic effects of OC

use. This may be of particular importance in women with existing disorders of lipid or carbohydrate metabolism, or those otherwise at risk for CVD. Based on present understanding of the role of lipids and lipoproteins in the pathogenesis of CVD, OC-related reductions in HDL may be of greatest concern with regard to CVD risk. This reduction is greatest with OCs containing more androgenic progestins, particularly at high doses. However, with commonly used low dose OC preparations, especially those containing newer and less androgenic progestins, the magnitude of HDL and other lipoprotein changes are generally small, and are likely to be of minimal clinical significance in healthy non-smoking women.

VI. Acknowledgements

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Table 3-3. Percentage change in lipids and lipoproteins: Baseline to 1 year

		% change		
	Control	*ED*† *(1 mg)*	*NEA*† *(1 mg)*	*NG*† *(0.5 mg)*
Total cholesterol	-2	9*	7*	8*
Triglycerides	-5	57*	45*	32*
LDL	0	10*	6	18*
HDL	-3	1	32	-13*
HDL_2	-1	4	-3	-27*
HDL_3	-2	5	11*	5
Apolipoprotein A-I	-4	11*	9*	-9
Apolipoprotein A-II	-4	17*	18*	12*

From Lipson A, et al (21).
*$p < 0.05$.
† + EE (50 μg)

Table 3-2. Plasma Lipoprotein Concentrations*

Exposure Group		*n*	*Serum Lipids, mean (mg/ld)*			
			Total cholesterol	HDL	LDL	Triglycerides
Nonuser		192	192.5	57.5	121.0	84.2
Past User		1123	198.4	59.7	124.2	86.7
Current User						
Estrogen (mg)	NE (mg)					
≥ 0.05	< 1.5	106	201.8	60.0	121.1	123.8
≥ 0.05	> 1.5	12	209.6	53.0	136.4	120.9
> 0.05	< 1.5	72	208.3	63.3	123.5	129.0
> 0.05	>1.5	19	215.4	58.8	135.4	127.1

From Perlman JA, et al. (18). Reprinted by permission of Greenwood Publishing Group, Inc., Westport, CT.
*Adjusted for age, body mass index, cigarettes and caffeine use.

Table 3-1. Lipids and Lipoproteins: OC Users Versus Nonusers

	Estrogen (mg)	Progestin (mg)	*n*	*Serum Lipids, mean (mg/ld)*			
				Total cholestrerol	Triglyceride	HDL	LDL
Nonusers	—	—	642	180 ± 30.9	79 ± 37.0	55 ± 15.4	113 ± 27.8
Ortho-Novum	ME (0.05-0.1)	NE (1-2)	146	193 ± 25.9*	121 ± 47.7*	49 ± 14.5*	118 ± 26.7
Norlestrin	EE (0.05)	NEA (1-2.5)	41	203 ±45.4*	120 ± 57.3*	53 ± 14.3	134 ± 41.7
Ovral	EE (0.05)	NG (0.5)	76	194 ± 36.5*	109 ± 43.3*	45 ± 13.4	133 ± 35.6*

Modified from Wahl P., et al (17).
ME, mestranol
* Difference versus nonusers significant, $p < 0.05$.

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