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Journal Vol: 106
Journal Issue:
Journal Year: 1984
Article Title: The effects of hormone implants on serum lipoproteins and steroid hormones in bilaterally oophorectomised women
Article Author: Farish
Article Pages: 116-20

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Acta Endocrinologica 1984, 106: 116–120

The effects of hormone implants on serum lipoproteins and steroid hormones in bilaterally oophorectomised women

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Abstract. Serum lipoproteins were measured over a period of 6 months in 14 oophorectomised women treated with oestrogen implants (50 mg oestradiol-17β) and 17 oophorectomised women treated with oestrogen/testosterone implants (50 mg oestradiol-17β, 100 mg testosterone). Both types of implant caused only minimal changes in lipoprotein metabolism. Low density lipoprotein (LDL) cholesterol decreased with both types of implant and high density lipoprotein (HDL) cholesterol rose with the oestrogen implants. HDL subfractions were also measured. The oestrogen implants caused a transient rise in HDL_2 cholesterol levels at 2 months and a slower rise in HDL_3 cholesterol. The oestrogen/testosterone implants had no effect on HDL fractions. The results indicate that hormone implants do not cause the profound changes in lipoproteins associated with oral hormone therapy.

Considerable interest has been shown in the lipid altering properties of hormone replacement therapy in post-menopausal women because of the link between lipoproteins and cardiovascular disease (Gordon et al. 1977; Miller et al. 1977). Oestrogens, when administered orally have been shown to cause significant alterations in lipoproteins (Tikkanen et al. 1978; Silfverstolpe et al. 1980). However, Fåhraeus et al. (1982) found that the changes in lipoproteins caused by oestradiol-17β taken orally were not in evidence when it was administered as a cream and Buckman et al. (1980) found that parenteral depo-oestradiol cypionate had little effect on serum lipoproteins. To date there has only been one detailed report dealing with the effects on lipoproteins of oestrogens administered as a subcutaneous (sc) implant. Brook et al. (1982) studied 3 women for a period of 12 weeks and noted profound changes in serum lipoproteins, particularly in high density lipoprotein (HDL) and its subclasses.

In this study we describe changes in lipoproteins over a period of 6 months in 31 oophorectomised women who were receiving hormone replacement therapy by way of sc implants. Two types of implant were used, one containing only oestradiol-17β, the other an oestradiol/testosterone mixture, since it has been suggested (Studd et al. 1977) that the inclusion of testosterone improves libido in postmenopausal women.

Patients and Methods

Thirty-one women attending menopausal clinics at the Western Infirmary and Stobhill Hospital, Glasgow who were suffering from climacteric symptoms were treated with hormone implants. They were aged between 36 and 54 years (mean age 46.4 years) and all had undergone hysterectomy and bilateral oophorectomy for non-malginant conditions. At least 6 weeks had elapsed post-operation prior to commencing treatment and informed consent was obtained in all cases before implant insertion. None of the women had received any hormone therapy prior to commencing treatment nor were taking any drug liable to interfere with lipid metabolism. None

Table 1.
Oestradiol and testosterone levels (mean ± SEM) in postmenopausal women treated with hormone implants.

	Oestradiol implants			Oestradiol/testosterone implants		
	n	Oestradiol (pmol/l)	Testosterone (nmol/l)	n	Oestradiol (pmol/l)	Testosterone (nmol/l)
Baseline	14	*	1.45 ± 0.16	17	**	2.36 ± 0.24
2 months	14	343 ± 39	1.55 ± 0.14	17	332 ± 24	6.62 ± 0.79
4 months	14	339 ± 21	1.56 ± 0.17	16	329 ± 25	4.74 ± 0.34
6 months	14	369 ± 45	1.59 ± 0.13	17	336 ± 27	2.88 ± 0.23

* Ten women had oestradiol levels less than 100 pmol/l. The other 4 had levels less than 200 pmol/l.
** Twelve women had oestradiol levels less than 100 pmol/l. The other 5 had levels less than 175 pmol/l.

of the women had renal or hepatic abnormalities before or during treatment as indicated by routine biochemical tests.

The women were randomly divided into two groups. Fourteen women were given oestrogen implants (50 mg oestradiol-17β) and the remaining 17 were given oestrogen/testosterone implants (50 mg oestradiol-17β, 100 mg testosterone).

Blood was obtained, after a 14 h fast, prior to insertion of the implant and 2, 4 and 6 months post implantation. Serum was separated by centrifuging at 1000 × *g* for 10 min at 4°C. An aliquot of serum was stored at 4°C for a maximum of 5 days prior to lipoprotein analysis and a further aliquot stored at −20°C for steroid analysis.

Serum lipoproteins were separated into their density classes by ultracentrifugation (Airfuge, Beckman Instruments Ltd., High Wycombe, England) as previously described (Farish et al. 1983). In addition, total HDL and HDL subfractions were measured in 10 of the women who had oestrogen implants and 9 who had oestrogen/testosterone implants using the method described by Eyre et al. (1981). Cholesterol concentrations were estimated manually using an enzymatic technique (Allain et al. 1974). Total serum triglyceride concentrations were also quantitated enzymatically (Bucolo & David 1973) using a Gemini centrifugal analyser (Electro-Neucleonics Inc. Breda, The Netherlands).

Serum oestradiol was measured by a radioimmunoassay (RIA) which used a rabbit antiserum raised against oestradiol-6-O-carboxymethyloxime-BSA, [^{3}H]oestradiol and a double antibody separation. The sensitivity of the system was 100 pmol/l and the inter-assay CV was 11%. Serum testosterone was also measured by RIA using a double antibody system employing a rabbit antiserum raised against testosterone-3-O-carboxymethyloxime-BSA and an [^{125}I]histamine conjugate of testosterone-3-O-carboxymethyloxime as radioligand. The assay had a sensitivity of 0.5 nmol/l and an inter-assay precision of 10%.

The results obtained were analysed by standard statistical techniques. Lilliefors' test (Conover 1975) was used to ascertain whether the sample data were normally

Table 2.
Lipoprotein levels (mean ± SD) in postmenopausal women treated with oestrogen-only implants.

	n	Total triglyceride (mmol/l)	Total cholesterol (mmol/l)	VLDL cholesterol (mmol/l)	LDL cholesterol (mmol/l)	HDL cholesterol (mmol/l)
Baseline	14	1.24 ± 0.59	6.21 ± 0.90	0.37 ± 0.19	4.24 ± 0.19	1.59 ± 0.19
2 months	14	1.18 ± 0.37	6.08 ± 1.08	0.27 ± 0.11	4.10 ± 1.06	1.71 ± 0.22*
4 months	14	1.19 ± 0.61	5.89 ± 0.93*	0.34 ± 0.18	3.87 ± 0.90**	1.67 ± 0.17
6 months	14	1.14 ± 0.52	6.02 ± 1.22	0.35 ± 0.16	3.97 ± 1.16	1.70 ± 0.24*

* Significantly different from baseline $P < 0.05$. ** Significantly different from baseline $P < 0.01$.

Table 3.

Lipoprotein levels (mean ± SD) in postmenopausal women treated with oestrogen/testosterone implants.

	n	Total triglyceride (mmol/l)	Total cholesterol (mmol/l)	VLDL cholesterol (mmol/l)	LDL cholesterol (mmol/l)	HDL cholesterol (mmol/l)
Baseline	17	1.48 ± 0.42	6.11 ± 0.93	0.48 ± 0.20	4.20 ± 0.89	1.45 ± 0.29
2 months	17	1.29 ± 0.43	5.74 ± 0.77**	0.39 ± 0.17	3.85 ± 0.64**	1.48 ± 0.29
4 months	16	1.26 ± 0.44	5.81 ± 0.75*	0.38 ± 0.22	3.94 ± 0.68*	1.47 ± 0.29
6 months	17	1.27 ± 0.35	5.78 ± 0.95*	0.39 ± 0.18	3.88 ± 0.80**	1.51 ± 0.34

* Significantly different from baseline $P < 0.05$. ** Significantly different from baseline $P < 0.01$.

distributed. Lipoprotein concentrations during treatment were compared with baseline values using Student's paired *t*-tests when the data were normally distributed and Wilcoxon's matched pairs signed ranks tests when they were not.

Results

Oestradiol and testosterone levels for the 31 women are shown in Table 1. In both groups oestradiol levels rose in the first 2 months to pre-menopausal levels at which they remained for the rest of the trial. Testosterone levels remained constant in the oestrogen-only group for the whole of the 6 months. In the oestrogen/testosterone group, they rose in the first 2 months then gradually fell to pre-treatment levels at 6 months.

Lipoprotein levels for the two groups of women are shown in Tables 2 and 3. Neither implant had any marked effects on lipoproteins. The oestrogen implants caused a reduction in low density lipoprotein (LDL) cholesterol and a small increase in HDL cholesterol. The only significant change caused by the oestradiol/testosterone implants was a reduction in LDL levels.

Table 4 shows total HDL, HDL_2 and HDL_3 levels for 10 of the women who had oestrogen implants. There was a temporary elevation of HDL_2 cholesterol levels at 2 months and a slower but more sustained increase in HDL_3 cholesterol levels. The levels of total HDL and the HDL subfractions were unaffected by the oestrogen/testosterone implants (Table 5).

Discussion

Oral natural oestrogens have been shown to elevate HDL cholesterol levels and reduce LDL cholesterol levels (Tikkanen et al. 1978; Silfverstolpe et al.

Table 4.

Total HDL and HDL subfractions (mean ± SD) in postmenopausal women treated with oestrogen-only implants.

	n	HDL cholesterol (mmol/l)	HDL_2 cholesterol (mmol/l)	HDL_3 cholesterol (mmol/l)
Baseline	10	1.61 ± 0.18	0.48 ± 0.12	1.05 ± 0.16
2 months	10	1.69 ± 0.19	0.62 ± 0.21*	1.03 ± 0.13
4 months	10	1.70 ± 0.19	0.50 ± 0.14	1.16 ± 0.15**
6 months	10	1.69 ± 0.27	0.46 ± 0.15	1.16 ± 0.13

* Significantly different from baseline $P < 0.05$.
** Significantly different from baseline $P < 0.01$.

Table 5.
Total HDL and HDL subfractions (mean ± SD) in postmenopausal women treated with oestrogen/testosterone implants.

	n	HDL cholesterol (mmol/l)	HDL_2 cholesterol (mmol/l)	HDL_3 cholesterol (mmol/l)
Baseline	9	1.42 ± 0.24	0.37 ± 0.20	0.99 ± 0.21
2 months	7	1.44 ± 0.28	0.43 ± 0.17	0.94 ± 0.10
4 months	9	1.41 ± 0.21	0.45 ± 0.17	0.93 ± 0.12
6 months	9	1.35 ± 0.32	0.33 ± 0.15	0.93 ± 0.22

1980; Fåhraeus et al. 1982). However, these reports were contradictory regarding their effects on triglyceride and very low density lipoprotein (VLDL) cholesterol. Androgens reduce HDL and VLDL cholesterol and increase LDL cholesterol (Furman & Howard 1962; Solyon 1971).

We have shown that implants do not produce the profound alterations in serum lipids produced by oral therapy. The only significant alterations were the lowering of LDL cholesterol by both types of implant and the increasing of HDL cholesterol by the oestrogen implants and none of these changes were large. Fåhraeus et al. (1982) investigating the effects of parenteral oestradiol-17β, produced similar results in that they found a gradual decrease in LDL cholesterol levels. However, they found no changes in HDL cholesterol levels.

The effects of natural oestrogens and androgens on HDL subfractions are not well documented. Brook et al. (1982) reported oestradiol-17β implants caused marked increases in both HDL_2 and HDL_3 cholesterol over a period of 3 months. This contrasts with our finding of small increases in HDL subfractions. However, Brook et al. (1982) studied only 3 women and used implants containing double the amount of oestradiol-17β used in the present study. We found the addition of testosterone to the implants to have only a slight effect on the HDL subfraction changes, preventing the small rises produced by oestrogen alone.

It is not as yet clear why parenteral oestrogen therapy should differ so markedly from oral therapy in its effects since the oestradiol levels we found with the implants were comparable to those produced by oral therapy (Lind et al. 1979). A likely explanation cited by previous workers (Buckman et al. 1980; Fåhraeus et al. 1982) is that oral oestrogens lead to peaks in intrahepatic and plasma concentrations and these cause the marked changes in lipoprotein levels.

In a recent study carried out on a similar group of bilaterally oophorectomised women using exactly the same therapy regimens, Dow et al. (1983) found that both types of implant were equally effective in reducing the severity of psychological, somatic and vasomotor symptoms and significantly improved libido. Their results indicated that the additional use of testosterone offers no advantage over oestradiol alone in the treatment of sexually unresponsive women. There is little to choose between the two types implant with regard to their effects on the lipoprotein risk factors for coronary heart disease. Although the oestrogen implants caused a small increase in HDL cholesterol not in evidence with the combined implant, this was mainly due to a slow rise in HDL_3 cholesterol, the rise in the anti-atherogenic HDL_2 fraction being transient. In addition, testosterone supplementation appeared to slightly enhance the LDL cholesterol-lowering effect of oestradiol.

In conclusion, we have confirmed that oestrogen implants affect lipoproteins in a similar manner, but to a much lesser extent than oral oestrogen therapy and that the addition of testosterone to the implants, although of dubious clinical value, has little further effect on lipoprotein status.

References

Allain C C, Poon L S, Chan C S G, Richmond W & Fu P C (1974): Enzymatic determination of total serum cholesterol. Clin Chem 20: 470–475.

Brook J G, Aviram M, Oettinger M & Sharf M (1982): The effects of oestrogen implants on high density lipoprotein and its subfractions in women in their pre-mature menopause. Maturitas 4: 257–265.

Buckman M T, Johnson J, Ellis H, Srivastava L & Peake G T (1980): Differential lipemic and proteinemic response to oral ethinyl estradiol and parenteral estradiol cypionate. Metabolism 29: 803–805.

Bucolo G & David H (1973): Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 19: 476–482.

Conover W J (1975): Practical nonparametric statistics, p 302–305. John Wiley & Sons, New York.

Dow M G T, Hart D M & Forrest C A (1983): Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparative study. Br J Obstet Gynaecol 90: 361–366.

Eyre J, Hammett F & Miller N E (1981): A micro-method for the rapid ultracentrifugal separation of human plasma high density lipoprotein subfractions HDL_2 and HDL_3. Clin Chim Acta 114: 225–231.

Fåhraeus L, Larsson-Cohn U & Wallentin L (1982): Lipoproteins during oral and cutaneous administration of oestradiol-17β to menopausal women. Acta Endocrinol (Copenh) 101: 597–601.

Farish E, Fletcher C D, Hart D M, Kitchener H & Sharpe G I. M (1983): A long term study of the effects of norethisterone on lipoprotein metabolism in menopausal women. Clin Chim Acta 132: 193–198.

Furman R H & Howard R P (1962): Effects of androsterone and triiodothyronine on serum lipids and lipoproteins, nitrogen balance and related metabolic phenomena in subjects with normal and decreased thyroid function, with hyperglyceridemia and/or hypercholesterolemia. Metabolism 11: 76–93.

Gordon T, Castelli W P, Hjortland M C, Kannel W B & Dawber T R (1977): High density lipoprotein as a protective factor against coronary heart disease. Am J Med 62: 707–714.

Lind T, Cameron E C, Hunter W M, Leon C, Moran P F, Oxley A, Gerrard J & Lind U C G (1979): A prospective, controlled trial of six forms of hormone replacement therapy given to postmenopausal women. Br J Obstet Gynaecol 86, Suppl 3: 1–29.

Miller N E, Forde O H, Thelle D S & Mjos O (1977): The Tromso heart study. High-density lipoprotein and coronary heart disease: a prospective case-control study. Lancet 1: 965–968.

Silfverstolpe G, Gustafson A, Samsioe G & Svanborg A (1980): Lipid metabolic studies in oophorectomized women. Effects induced by two different estrogens on serum lipids and lipoproteins. Gynecol Obstet Invest 11: 161–169.

Solyon A (1971): Effects of androgens on serum lipids and lipoproteins. Lipids 7: 100–105.

Studd J W W, Collins W P, Chakravarti S, Newton J R, Oram D & Parsons A (1977): Oestradiol and testosterone implants in the treatment of psychosexual problems in the postmenopausal woman. Br J Obstet Gynaecol 84: 314–315.

Tikkanen M J, Nikkila E A & Vartiainen E (1978): Natural oestrogen as an effective treatment for type II hyperlipoproteinaemia in postmenopausal women. Lancet 2: 490–491.

Received on September 28th, 1983.