Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Effect of hormones on Serum Lipid Lipoprotein Profile in Females of Reproductive Age Group.

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Received: February 2018
Accepted: February 2018

ABSTRACT

Background: Oral contraceptives can induce changes in lipid, lipoprotein and carbohydrate metabolism. This study is done to find out basal lipid profile in females of reproductive age group using sequential hormone therapy and with low dose estrogen combinations pills; and to study the changes in lipid profile after 3 months use of sequential hormone therapy and with low dose estrogen combination pills. **Methods:** Total 40 females were taken of 18-40years of reproductive age group ,subjects were divided into two groups. Group A: 20 females were subjected to sequential hormones therapy. Group B: 20 females were subjected to combined oral contraceptive pill "Mala N". **Results:** In Group A there was significant rise in serum cholesterol, serum TGs ,LDL, VLDL levels and LDL:HDL ratio. HDL shows fall in there levels. In Group B there was no significant change in all lipid parameters. **Conclusion:** There is substantial degree of metabolic changes in lipid lipoprotein profile in females with use of sequential hormones .With use of low dose estrogen and progesterone pills, there is no such deleterious effect on lipid profile and so it can be used for prolonged period. As the indications of use of sequential hormones in females of reproductive age group are now increasing in gynecological practice it would be advisable to decrease the dose of estrogen to avoid its effects on lipid profile.

Keywords: STGs:Serum triglycerides. LDL:Low density lipoproteins . VLDL: Very low density lipoproteins .HDL: High density lipoproteins . SC:Serum cholesterol. COCs:Combined oral contraceptive pills.

INTRODUCTION

Oral contraceptive agents can induce substantial metabolic changes that resemble those seen in persons at increased risk for premature coronary heart disease.[1] These changes include raised serum TGs and LDL-C levels , reduced HDL -C levels impairment of glucose tolerance and elevated insulin levels.[2,3] It is observed that unopposed estrogen therapy leads to endometrial hyperplasia and so increase risk of endometrial carcinoma. Sequential and combination regimes as compared to unopposed estrogen treatment has the advantage of not inducing hyperplasia. It is believed that sequential region can also remove the estrogen related hyperplasia back to normal endometrium. Low dose hormonal contraceptive did not pose the damage of increasing the incidence of cardiovascular and thromboembolic disease.[4] Sitruk-Ware stated that desogestrel and other new progestins which are non-androgenic,[5] have no negative effect on the lipid profile. Lello et al,[6] observed that combined ethinyl estradiol (20ug) and levonorgestrel (100ug) has no effect on lipid profile. The oral contraceptive hormones, introduced in 1960, have undergone much modification. Worldwide, the contraceptive pills are used by 100 millions of women in child bearing age and about 11.6 million women of United States used combined oral contraceptive pills (COCPs).About 80% of child bearing age American women have used oral contraceptives in their life at some time.[7]

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MATERIALS AND METHODS

The present study was prospective analytical study carried out in the department of Obstetrics and Gynecology in Muzaffarnagar Medical College & Hospital from June 2016 to December 2017.

Subjects

All the women of reproductive age group (15-45 yrs) who were subjected to sequential hormone therapy and combination of oral pills were choosen as subjects. Total no.of subjects studied were 40. All the subjects were completely studied with detailed history and physical check-up. Following patients were excluded from the study.

- Patient with liver disease, ischemic heart disease, hyperlipidemia, diabetes, renal disease, hypertension, acute and recurrent vascular thrombosis.

- Patient who has already taken hormones prior to the commencement of the hormone therapy.
- Patient whose bases endometrial histology showed evidence of endometrial hyperplasia and adenocarcinoma.
- Patients on drugs those are liable to interfere with lipid metabolism and lipoproteins levels in the blood.

The cases were divided into two groups.

GROUP–A: Women between age 18-40 years who were subjected to sequential hormone therapy. Lynoral 0.05 mg (Ethinyl estradiol) once daily from day 5th to day 25th of menstruation and Primolut N (Norethisterone acetate 5mg) thrice daily from day 16th to day 25th of the cycle and after withdrawal hormones started again and given for three such cycles .

GROUP–B: Women between age 18-40years who were subjected to combined oral contraceptive pills 'MALA–N' supplied by government of India under its family planning program. All the participants received oral and written information about the trial.

Following special investigations were performed

- Serum Total cholesterol
- Serum Triglycerides
- Serum Lipoprotein profile (HDL,LDL,VLDL)

Method of collection of blood samples

5 ml of blood was withdrawn from antecubital vein of the female in recumbent position with all aseptic precautions.

- After 12- 14 hrs of fasting
- After 10 min of supine rest
- After withdrawal blood was allowed to settle for 30 min and then centrifuged and serum was preserved with standard precautions.

Period of collection of blood sample

1. At first visit to the hospital.
2. In 1st , 2nd & 3rd month after hormonal therapy.

Estimation of lipid factors

Various lipid factors Serum total cholesterol (STC), Serum triglycerides (STG), High density lipoproteins were estimated by diagnostic chemical kits while Low density lipoprotein (LDL),Very low density lipoprotein (VLDL) and LDL:HDL were derived from values of above mentioned lipid by standard formula.

RESULTS

From [Table 2] it is evident there is rise in levels of serum cholesterol after 1 month, 2 months, 3 month use of hormones in both the group but rise is not statistically significant in Group B while it is significant in Group A .

In Group A significant values are –

0 vs III t= 4.94 ($p \leq 0.001$)

I vs III t= 3.74 ($p \leq 0.01$)

Table 1: Distribution of patients in two groups.

Group	Hormone therapy	No. of subjects	Age (year)	Percentage
Group A	Sequential hormones	20	18-38	50%
Group B	Combined oral pills	20	18-40	50%

Table 2: Effect of sequential hormone therapy on Total Serum Cholesterol concentration (Mean ± SD) in mg/dl in Group A and effect of combined oral pills on total serum cholesterol concentrations (Mean ± SD) in mg/dl in Group B

Groups ↓	Zero	1 Month	2 Month	3month
A (n= 20)	150.40 ± 24.97	150.25 ± 26.38	173.10± 24.03	190.18± 25.85
B (n=20)	166.52 ± 38.59	179.10±39. 76	180.09±39. 02	181.23±38. 63

So we can say that rise in cholesterol was highly significant after 3months of use of sequential hormones while it is insignificant after 3months of use of combined oral pills when the values are compared with basal as well as 1 month therapy

Table 3: Effect of sequential hormone therapy on Serum Triglycerides level (mean± SD) in Group A and effect of combined oral pills on serum triglycerides in Group B (mean ±SD) mg/dl.

Groups	Zero	1 month	2 month	3 month
A	92.27 ±32.6	102.03± 35.89	113.50 ±43.60	127.6± 56.36
B	90.61± 18.79	91.04 ±19.16	92.64 ±19.07	93.26 ±19.28

From [Table 3] it is evident that serum triglycerides level show rise in trend in both the groups but the rise is significant in Group A. In Group A rise in serum triglyceride is significant and significant values are:

0 vs III = t=2.35 ($p < 0.05$)

Table 4: Effect of sequential hormone therapy on Serum HDL levels in Group A and effect of combined oral pills on Serum HDL levels Group B (mean ± SD) mg/dl in both groups.

Groups	Zero	1 month	2 month	3 month
A	55.40 ±12.69	50.45± 11.89	45.42 ± 11.82	38.52 ± 11.32
B	67.54± 14.22	66.77 ± 14.91	74.80 ± 15.35	63.72 ± 16.69

From [Table 4] it is evident that there is fall in serum HDL levels with sequential and combined oral pills therapy but the fall is significant only with sequential hormonal therapy. Significant values are

0 – II t=2.57 ($p < 0.05$)

0 – III t=4.43 ($p < 0.001$)

I – III t=3.51 ($p < 0.01$)

So when basal values of the serum HDL in Group A compared with the values after I ; II ; III months of the therapy it was seen that fall in serum HDL levels

was statistically significant after 2 months and 3 months of therapy when values of 1 month therapy are compared with values of 3 month therapy they were also found to be statistically significant.
In Group A there was fall in serum HDL level but it was highly insignificant

Table 5: Effect of sequential hormones and combined oral pills on Serum LDL level (mg/dl) in Group A and Group B (mean ± SD)

Groups	Zero	1 month	2 month	3 months
A	79.62 ±27.50	90.37± 26.16	101.70 ±20.97	128.54±40.91
B	87.57±40.77	94.89± 41.92	97.95±42.23	100.23±43.03

From [Table 5] it is evident that serum LDL level show rise in trend in both the groups. Values of zero level are are compared with values of 1 , 2 , 3 month therapy in both the groups and it was seen that the levels show significant rise in Group A after 2 and 3 months therapy while the values in group B show insignificant change in LDL levels. Comparison between values of 1 month and 3 month was also statistically highly significant in Group A. Significant values in Group A are
0 - II = t=2.84 ($p < 0.01$)
0 – III t= 4.42 ($p < 0.001$)
I – III t = 3.50 ($p < 0.01$)

Table 6: Effect of sequential hormones and combined oral pills on Serum VLDL concentration level (mg/dl) in Group A and Group B (mean ± SD)

Groups	Zero	1 month	2 month	3 month
A	19.30 ± 6.44	20.94 ±6.99	22.83 ±8.64	25.62±9.99
B	17.88±3.77	18.36±3.74	18.40±3.82	18.56±3.63

From [Table 6] it is evident that serum VLDL level show rise in trend in both the groups but the values are significantly raised in Group A only. It is seen that rise in serum VLDL was statistically significant after 3months of use of sequential hormone while the rise after 1st and 2nd month of therapy was not significant when compared with zero values. Significant values are
0 – III t= 2.37 ($p < 0.05$)

Table 7: Effect of LDL: HDL ratio pills in Group A and Group B (mean ± SD) after use of sequential hormones and combined oral hormones respectively mg/dl

Groups	Zero	1 month	2 month	3 month
A	1.48 ±0.62	1.94 ±0.91	2.56 ±1.02	3.57 ±1.47
B	1.45 ±0.80	1.50 ±0.88	1.72 ±1.05	1.64 ±1.25

So we see from [Table 7] that LDL: HDL ratio increases in both the groups but again the values were not significantly changed in group B.
In Group A the values are satistically significant after 1 month therapy when compared with zero value. LDL: HDL ratio is highly significant increase after 2 months and 3 months use
0 – I t =2.08 $p < 0.05$)
0 – II t= 4.15 ($p <0.001$)
0 –III t= 5.97 ($p < 0.001$)
I –III t = 4.28 ($p <0.001$)

DISCUSSION

Contraceptives hormones most commonly prescribed as oral contraceptives agents which can induce metabolic changes like raised serum TGs, LDL cholesterol levels reduce HDL levels (Valanis et al., 2003)[8] The Womens Health Initiative (WHI) found that women taking estrogen(conjugate equine estrogen) plus progestin (medroxyprogesteron eacetate) were at increased risk for myocardial infarction ,stroke ,venous thromboembolism and breast cancer as compared with women taking placebo.[9] The present study supports the earlier studies on lipid profile (Emokpae et al., 2010;Abdel-Barry et al., 2011).[10,11] Combined oral contraceptives affects a variety of metabolic factors including hemostatic variables and estrogen-sensitive liver proteins and these effects can be modulated by the type of estrogen and progestin in a given combination(Sitruk-Ware and Nath, 2011). OCs containing levonorgestrel was associated with an almost four times higher risk of venous thrombosis as compared to non-users (Van Hylckama Vlieg et al., 2009). The injectable oral contraceptives have also been reported to increase the levels of triglycerides, total cholesterol, High Density Lipoprotein (HDL) cholesterol in the serum (Godsland et al., 1990). The latest advance in the 30-year evolution of oral contraceptives (OCs) is the development of three new progestogens: desogestrel, norgestimate, and gestodene. These three new agents are derivatives of levonorgestrel, a gonane hormone, and have been used to develop pills that provide effective pregnancy prevention at lower doses than oral contraceptives using the older steroids.[12]

Total serum cholesterol

In group A we found significant rise in STC levels after sequential hormone therapy for 3 months. These findings are consistent with findings of Arora et al (1989) observed a significant rise in serum cholesterol concentration with use of sequential pills.[13]
In group B an insignificant rise was seen with low dose combination pills after 3 months of use. Barton et al (1970) studied effect of different combination pills on serum lipid levels there was a significant rise in serum cholesterol level with high dose of estrogen

pills while rise was insignificant in females using low dose estrogen or only progestin pills.

Serum triglyceride

In group A a significant rise in STGs were observed these findings are consistent with findings of Stocks and Wynn (1971) and Kalhkoff et al (1982). Stocks found that there was a significant rise in STGs levels from 68mg/dl to 110mg/dl. Kalhkoff et al explained that progesterone increases storage of serum triglyceride due to stimulation of lipoprotein lipase which cause hydrolysis of circulating triglyceride and there consequent storage.

In group B there was insignificant rise in STG levels with use of low dose combination pills and these findings correlate with observation of Glueck et al (1973), Spellacy et al (1976),Wallace et al (1979). Wynn (1979) studied the effect of oral contraceptive pills containing (30 – 150 ug) ethinyl estradiol and he observed that rise in STG was statistically significant in high and medium dose pills while it was insignificant in low dose estrogen pills. Wallace et al found that plasma triglyceride levels increased significantly with increasing dose of estrogen. The levels of plasma TGs were significantly elevated in both younger and older women using sex hormone either in sequential or combination forms. The rise was highest with high estrogen combination and sequential therapy and it shows that estrogen is related with rise in TGs levels. Arora et al (1988) found an insignificant rise in STG levels after 3 and 6 months of use of low dose combinations pills. Ethinyl estradiol increases hepatic secretion of TGs rich lipoproteins.

Serum high density lipoprotein

HDL is divided into two subfractions HDL2 and HDL3 . The HDL2 subclass may be more sensitive indicator of risk than total HDL cholesterol.[14] Low level of HDL increase the risk of coronary heart disease especially in women.[15,16] Ethinyl estradiol raises HDL cholesterol levels conversely progestin can lower HDL cholesterol levels by increasing hepatic lipase activity.[17-20] Generally combination drugs lowered HDL2 levels and increased HDL3 levels

In group A a significant fall is seen in HDL level. This finding correlates well with observation of Aurell and Crammer (1966) who observed significant fall in HDL level with high dose estrogen pills.[21] Arora et al (1989) found a significant fall in HDL levels in females of reproductive age group using sequential hormones while no effect was observed in menopausal and postmenopausal females.

In group B an insignificant fall is seen in HDL levels in cases who used low dose estrogen and high dose progestins combination pills. Krauss et al in his studies found that change in HDL levels depends upon relative amount of estrogen and progestins. Arora et al (1988) found no significant fall with use of 30µg/1mg EE/ norethisterone acetate combination pills.

Serum LDL and VLDL

In Group A there was a significant rise in serum LDL and VLDL levels with use of sequential hormones. Triglycerides and VLDL reflects parallel picture to each other. The estrogen component of OCs has been reported to increase the production of Very Low Density Lipoprotein (VLDL) and High Density Lipoprotein (HDL) but reduce the level of low density lipoprotein (Sitruk-Ware,2006).[22,23] The reduction in the doses of Levonorgestrel/ethinyl estradiol containing contraceptives from 30-20 µg (EE) and that of 150-100 µg (levonorgestrel) resulted in the less adverse effect on the lipid profile and have been suggested to lower the incidence of thrombosis as compared to other EE based contraceptives (Skouby et al., 2005).[24] The findings are consistent with ,(Molitch et al.,1974), (Gupta et al.,1976), (Arora et al.,1989). Aurell and Molitch observed a significant rise in serum LDL and VLDL levels and they attributed this rise to administration of exogenous estrogen.[25]

In group B there was no change in LDL and VLDL levels in females using low dose estrogen and high dose progesterone combination pills these findings are similar to observations of knop et al (1982) who studied the effects of six combination pills and found a parallel increase in VLDL levels with increasing dose of estrogen component

CONCLUSION

We concluded from our present study that there is substantial degree of metabolic changes in lipid lipoprotein profile in females of reproductive age group with use of sequential hormones resemble those seen in persons at increased risk for premature coronary heart disease. These changes are attributed to estrogen used in sequential hormones. With use of low dose estrogen and progesterone pills, there is no such deleterious effect on lipid profile and so it can be used for prolonged period. As the indications of use of sequential hormones in females of reproductive age group are increasing in gynecological practice it would be advisable to decrease the dose of estrogen to avoid its effects on lipid profile. All the women should be screened for lipid profile before starting COCs and followed up regularly to prevent the risk of cardiovascular diseases in these women and to decrease disease burden on the country.

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How to cite this article: Prabhakar M, Sharma I, Singh S. Effect of hormones on Serum Lipid Lipoprotein Profile in Females of Reproductive Age Group. Ann. Int. Med. Den. Res. 2018; 4(3):OGXX-OGXX.

Source of Support: Nil, **Conflict of Interest:** None declared