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# A STUDY COMPARING THE EFFECTS OF DIFFERENT ORAL CONTRACEPTIVES ON LIPID PROFILE

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## ABSTRACT

Compare changes in serum lipid profile induced by Monophasic and Triphasic oral contraceptive pills (OCP). 80women aged 18-38 years, BMI 17-29 $Kg/M^2$, regular menstrual cycles, no contraindication for usage of OCP, not had hormonal treatment, Triphasic containing 30-40-30 micrograms ethinylestradiol and 50-75-125micrograms levonorgestrel (21/7-day regimen) given to forty women, Monophasic containing 30µg ethinyloestradiol and 150µg levonorgestrel (21/7-day regimen) given to forty women. Fasting samples collected prior to treatment and after completion of 6 cycles. Total Cholesterol, Triglycerides, HDL Cholesterol and LDL Cholesterol were determined. In Monophasic OCP, LDL Cholesterol was significantly increased and HDL Cholesterol decreased significantly. Levonorgestrel in combined OCP is potent androgenic. They maintain high levels of levonorgestrel throughout the cycle, causing raised LDL and reduced HDL Cholesterol. In Triphasic OCP Triglycerides and HDL Cholesterol increased, LDL Cholesterol decreased significantly due to less progestin and more estrogenic dominance. Triphasic OCP cause favorable changes in plasma lipids. Monophasic OCP causes more disturbances in lipid metabolism suggesting that long term use could increase the risk of Coronary artery disease.

**KEY WORDS:** **Oral Contraceptives, Monophasic, Triphasic, Lipid Profile.**

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# INTRODUCTION

The hormone contraceptives include four basic types: combination oral contraceptives (COCs), injectables, progestin only pills (minipill, or POPs), and implants (Norplant). Of above combined estrogens and progestins and continuous progestin therapy without concomitant administration of estrogen are two types of preparations are used for oral contraceptives Over the last 30 years, combined oral contraceptives (COCs) have become one of the most commonly used forms of family planning world-wide. Billions of women have benefited from both the direct contraceptive and indirect health-related benefits of these medications. There are several different estrogens and even more progestins available, and there are many ways to combine them into pill formulations. Ethinylestradiol (EE) has been the most commonly used estrogen component. In order to reduce the side effects and increase the acceptability, the EE dose was gradually reduced to 30 micrograms (mcg) or less. The progestogen dose, though, cannot be reduced nowadays since further reduction may not prevent the LH-surge and thus allow ovulation. The different progestogens can be classified according to their steroid structure and to their timing of market introduction. These can be categorized into three tetracyclic structures: the pregnanes (derived from the progesterone molecule), the estranes (derivatives of testosterone) and the gonanes. Gonane progestogens are divided into two classes: the second-generation progestogens levonorgestrel (LNG) and norgestrel (NG) and third-generation progestogens desogestrel (DSG), gestodene (GSD) and norgestimate (NGM). The second-generation progestogens entered the market in the 1970s. Currently, LNG is probably the most widely used progestogen and predominantly combined with 30 µg EE. The combination agents are further divided into monophasic forms (constant dosage of both components during the cycle) and biphasic or triphasic forms (dosage of one or both components is changed once or twice during the cycle). Triphasic oral contraceptives have three different doses of hormones over a cycle of therapy, allegedly attempt to 'mimic' the rising and falling of estrogen and progesterone during the normal menstrual cycle [(16)]. This purportedly results in a more 'physiologic' approach and a lower total monthly steroid dosage compared to the older monophasic oral contraceptives. Studies suggesting a possible association between the use of combined oral contraceptives and an increased risk of cardiovascular disease have led to extensive investigations into the effect of oral contraceptives on lipid and carbohydrate metabolism, and on haemostasis. Since this association was originally suggested, the steroid dose in oral contraceptives has been significantly reduced and new progestogens have been developed. Triphasic formulations have been introduced which offer a well-balanced estrogen/progestogen ratio, allowing a further reduction in the progestogen dose per cycle, and thus helping to minimize unwanted metabolic and haemostatic effects. However, potential disadvantages of these formulations include an increased risk of pill-taking errors caused by the array of different color pills, the higher price of the pills and the possible higher incidence of accidental pregnancy[(4)]. The metabolic interactions of triphasic levonorgestrel, the first triphasic formulation to be introduced, have received particular attention. Levonorgestrel is the second generation drug, has moderate androgenic activity. They have a high binding affinity to the androgen receptor, making it difficult to eliminate some of the undesirable androgenic effects. Concerning lipids, most studies suggest that triphasic levonorgestrel has less metabolic impact than the monophasic formulation. The purpose this of study is to evaluate the effect of two formulations (monophasic and triphasic) of contraceptive medications containing different doses of ethinylestradiol and levonorgestrel on lipoprotein metabolism.

# MATERIALS AND METHODS

This study had the voluntary participation of 80 healthy women, aged 18-38 years ,BMI 17-29 $Kg/m^2$, regular menstrual cycles, no contraindication for usage of OCP, not taken any hormonal treatment, included in this study

after taking consent; done at Asram medical college, Eluru. Triphasic, containing 30-40-30 micrograms ethinylestradiol and 50-75-125 micrograms levonorgestrel (21/7-day regimen) given to forty women, Monophasic, containing 30 micrograms ethinyloestradiol and 150 micrograms levonorgestrel (21/7-day regimen) given to forty women. Fasting samples collected prior to treatment, after completion of 6 cycles. Total Cholesterol(TC) determined by cholesterol oxidase & POD enzymatic method, Triglycerides by GPO–POD enzymatic method, HDL Cholesterol by precipitating method, LDL Cholesterol calculated by friedewald formula.

## STATISTICAL ANALYSES

Statistical analysis done using Microsoft office excel 2007 paired T test and the results are expressed as mean and standard deviation (SD). $P < 0.05$ was considered statistically significant.

## RESULTS

In Monophasic OCP, Total Cholesterol and Triglycerides were not significantly altered before and after treatment. LDL Cholesterol was significantly increased ($p<0.05$), HDL Cholesterol decreased significantly ($p<0.05$). The results were shown table -1.

**Table 1**
***Biochemical variables analyzed in Monophasic COCs users***

| MONOPHASIC | | TOTAL CHOLESTEROL mg/dl | TRIGLYCERIDES mg/dl | LDL C mg/dl | HDL C mg/dl |
|---|---|---|---|---|---|
| Pre treatment | MEAN±SD | 154.42 ± 27.12 | 99.22 ± 17.68 | 115.20 ± 18.19 | 50.43 ± 9.58 |
| Post treatment | MEAN±SD | 164.25 ± 28.60 | 101.112±17.18 | 132.31 ± 17.4 | 41.621 ± 6.72 |
| | P value | 0.06 | 0.61 | 0.0003 | 0.0006 |
| | Inference | Non significant | Non significant | significant | Significant |

***In triphasic OCP, Total Cholesterol was not significantly altered. Triglycerides increased significantly (p<0.05). LDL Cholesterol decreased significantly (p<0.05). HDL Cholesterol increased significantly (p<0.05). The results were shown table -2***

**Table 2**
***Biochemical variables analyzed in Triphasic COCs users***

| TRIPHASIC | | TOTAL CHOLESTEROL mg/dl | TRIGLYCERIDES mg/dl | LDL C mg/dl | HDL C mg/dl |
|---|---|---|---|---|---|
| Pre treatment | MEAN±SD | 174.26±13.49 | 94.525 ± 13.38 | 114.56 ± 6.48 | 52.50 ± 7.28 |
| Post treatment | MEAN±SD | 179.73±18.35 | 111.925 ± 18.85 | 102.51 ± 18.38 | 58.31 ± 5.22 |
| | P value | 0.119175 | 0.000574 | 0.00035 | 0.00005 |
| | Inference | Non significant | significant | significant | significant |

## DISCUSSION

The female sex hormone, estrogen secreted by the ovaries and testis with involvement of placenta, adipose tissue, and adrenal glands plays crucial role in development and growth of cell proliferation and differentiation including development of reproductive system and secondary sex characteristics[9]. It is well known that ovarian hormones have a great effect on lipid metabolism. Unopposed estrogen replacement therapy beneficially affects the lipid profile in menopausal women by lowering total serum cholesterol and low density lipoprotein(LDL) cholesterol, and increasing high density lipoprotein(HDL) cholesterol, especially the HDL2 sub fraction[14,15]. Progestin administered alone induce hepatic lipase activity, increasing, in this way, the degradation of HDL-cholesterol;

whereas, the addition of progestin to estrogens tends to attenuate the increase in serum HDL-cholesterol and the decrease in LDL-cholesterol. These effects of progestins upon lipid profile seem to depend on their biochemical structures, doses and regimens. Early studies showed that norethisteroneacetate (NETA) or levonorgestrel had a strong detrimental effect upon lipid metabolism (20-30% reduction in HDL-cholesterol) so that they were labelled as androgenic. In our study, Monophasic users maintain high levels of levonogestrel throughout the cycle, causing raised LDL and reduced HDL Cholesterol, progestogens enhance VLDL/triglyceride degradation, resulting in increased hepatic supply of cholesterol [5] and down regulation of LDL receptors in the liver, and increased LDL release into the circulation and increase HDL catabolism [5]. Thus estrogen-induced elevation of HDL cholesterol levels was opposed by levonorgestrel in a dose-dependent manner. Ethinylestradiol increases hepatic secretion of triglyceride-rich lipoproteins [13]. The differences we found in triglyceride levels among users of combination oral contraceptives reflect the ability of the progestin component to oppose this increase. Triphasic oral contraceptives allegedly attempt to 'mimic' the rising and falling of estrogen and progesterone during the normal menstrual cycle. Effects of estrogens upon plasma lipids are due to their reduction in hepatic triglyceride lipase, that degrades HDL, and to their stimulation of HDL-cholesterol production and synthesis of apolipoproteinA-I. A decrease plasma LDL concentrations, may be due to up regulation of hepatic LDL receptors [7]. Estrogens also diminishes HDL catabolism [13].Unfortunately, estrogens induce an increase in the synthesis of very-low-density lipoproteins (VLDLs) leading to elevations in serum triglyceride levels [6], but also reduce the catabolism of VLDL to LDL by enhancing the VLDL uptake by the liver. The status of elevated serum triglyceride levels as an independent predictor of coronary heart disease is also uncertain[12]; elevated triglyceride levels are not associated with increased risk if HDL cholesterol levels are also high[8]. COCs containing synthetic progesterone and estrogen in their formulation are responsible for the inhibition of the natural production of the hormones by the ovaries [3]. Despite of the protective effect developed by the estrogen, progesterone may exert adverse influence on the metabolism of the lipids. There has been controversy, however, about the possible risks, including coronary heart disease and myocardial infarction [11], of this treatment. Androgenic progestogens, derived from testosterone, have greater interference in the beneficial alterations of estrogen over the lipid profile, since they promote a reversion in the increase of HDL due to an increase in the activity of hepatic lipases [1] it has been implicated as a risk factor for coronary heart disease [10], perhaps through the promotion of potentially adverse changes in lipid and carbohydrate metabolism [2]. Levonorgestrel combinations more strongly opposed the action of estrogen and did so in a dose-dependent manner.

## CONCLUSION

Triphasic OCP causes favorable changes in plasma lipids. Monophasic OCP causes more disturbances in lipid metabolism suggesting that long term use could increase the risk of Coronary artery disease**.**

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## REFERENCES

1. Crook D, Cust MP, Gangar KF, Worthington M, Hillard TC, et al Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on serum lipids and lipoproteins. Am J Obstet Gynecol 166: 950-955,(1992).
2. Frank Z. Stanczyk, David F. Archer. (Gestodene: A review of its pharmacology, potency and tolerability in combined

contraceptive preparations. Contraception 89:4, 242-252,(2014)
3. Frye CA An overview of oral contraceptives: Mechanism of action and clinical use. Neurology 66: 29-36, (2006)
4. Guillebaud, J.Postpartum contraception – unnecessary before three Week BMJ, 307, 1560-1561,(1993).
5. Khokha R, Huff MW, Wolfe BM: Divergent effects of d-norgestrel on the metabolism of rat very low density and low density apoprotein B. J Lipid Res 27: 699, 1986
6. Kissebah AH, Harrigan P, Wynn V: Mechanism of hypertriglyceridemia associated with contraceptive steroids. Horm Metab Res 5: 184, 1974
7. Kovanen PT, Brown MS, Goldstein JL: Increased binding of low density lipoprotein to liver membranes from rats treated with 17alpha-ethinyl estradiol. J Biol Chem 254: 11367, 1979
8. Maria I. Rodriguez, Alison B. Edelman. Safety and efficacy of contraception—Why should the obese woman be any different?. Reviews in Endocrine and Metabolic Disorders 12:2, 85-91, (2011)
9. Md ataul islam and achintya saha. Selectivity requirement of estrogen receptor ligand S: Modeling of furan and pyrazole derivatives Int J Pharm Bio Sci July; 3(3): (P) 359 – 371 International Journal of Pharma and Bio Sciences ISSN 0975-6299 ,(2012).
10. Myung-A Kim. Triglyceride and Cardiovascular Disease. Journal of Lipid and Atherosclerosis 2:1, 1,(2013)
11. Rachel E.J. Roach, Frans M Helmerhorst, Willem M. Lijfering, Ale Algra, Olaf M Dekkers, Rachel E.J. Roach. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, 2014.
12. Regine Sitruk-Ware, Anita Nath. Metabolic effects of contraceptive steroids. Reviews in Endocrine and Metabolic Disorders 12:2, 63-75.(2011)
13. Schaefer EJ, Foster DM, Zech LA, Lindgren FT, Brewer HB Jr, Levy RI. The effects of estrogen administration on plasma lipoprotein metabolism in premenopausal females . J Clin Endocrinol Metab; 57:262–7 (1983).
14. Srivastava, R.A.K., Baumann, D. and Schonfeld, G. In vivo regulation of LDL receptors by estrogen differs at the post-transcriptional level in rat and mouse. Eur. J. Biochem., 216,527-538.(1993)
15. Tikkanen, M., Nikkala, E.A., Kuusi, T. *et al* High density lipoprotein-2 and hepatic lipase: reciprocal changes produced by estrogen and norgestrel. J. Clin. Endocrinol. Metab.,54, 1113-1117, (1982).
16. Upton GV. The phasic approach to oral contraception: the triphasic concept and its clinical application.International Journal of Fertility; 28 :121–40, (1983).