# Comparison of CVD Risk Associated With the Long Term Use of Contraceptives in Young Females

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## ARTICLE INFO

## ABSTRACT

The purpose of the present study is to compare the extent of cardiovascular atherosclerotic risk associated with the lipid metabolism in women using hormonal contraceptives in urban population of low socio-economic group. Type of Study was cross sectional. Fifty-four young females of age ranging from 26-32 years maintained on Oral contraceptives (OC), Depo-medroxy progesterone (DMPA), Norethisterone (NET-EN), Implant and non hormonal intrauterine contraceptive device (IUCD) for at least one year were invited. Fasting blood samples were collected for the analysis of lipid parameters. Castelli indices I & II were also calculated to determine the CVD risk. All the results were entered in MS-Excel and mean ± standard deviation was calculated for each frequency. The result of Castelli indices showed that the use of OCs was associated with the highest atherogenic index followed by NET-EN, IUCD, DMPA and implant. The CVD risk may also be attributable to other life style factors as it was not drastically different among hormonal and non hormonal users. Though the risk in this group of young females maintained on contraceptives was found to be minimized because of good monitoring but continuation of hormonal methods might cause this slight predisposition to sub clinical CVD into a well defined atherosclerotic disease later in their lives. It is therefore recommended to use such methods under close monitoring and over the counter use of hormonal contraceptives should be discouraged.

## INTRODUCTION

Abnormal lipid profiles have been associated with major risk factor for cardiovascular disease (CVD) which is one of the most dominant causes of death in the world and is mainly due to arthrosclerosis (Philip *et al*., 2007). Cardiovascular diseases are the leading cause of adult mortality. Previous studies since last three decades have shown an association between the hormonal contraceptive use and cardiovascular disease (Castelli *et al*., 1998, Dorflinger *et al*., 2002, Spellacy *et al*., 1982).

Extensive use of hormonal contraception by females through their reproductive life has lead to the concern about the effects of oral contraceptives on risk factors for coronary heart disease. Oral contraceptive-induced changes in both carbohydrate and lipoprotein risk factors may contribute to an increased risk of coronary heart disease (Tikkanen *et al*., 1981).

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The effect of sex steroids on lipid metabolism depends on the type and dose of the compounds, the route of administration, and the duration of treatment. Therefore the composition of a hormonal contraceptive determines the resultant effect on lipids and lipoprotein (Kuhl *et al*., 1990).

Orally administered estrogens increase hepatic triglyceride synthesis and VLDL secretion. Estrogens increase the rates of elimination of LDL, VLDL and chylomicrons; suppress the synthesis of key enzymes of lipoprotein metabolism, hepatic and lipoprotein lipase, and increase synthesis of the principal apoprotein of HDL, apoAI (Godsland *et al*., 2004)

Oral contraception usage has been found to be associated with adverse findings in several metabolic, cardiovascular and inflammatory parameters, which is consistent with an increased future risk of cardiovascular and metabolic disease. These findings should invite more criticism of recent trends that encourage the prescription of oral contraceptives for years during reproductive life and especially in pre-menopausal women   (Morin *et al*., 2008).

In general, progestagens oppose estrogen effects on lipoproteins according to type and dose. In OC users this leads to a range of different lipoprotein profiles, which may differ from those evaluated with respect to vascular disease risk in population studies (Godsland *et al*., 2004). In a study by Berenson *et al*., 2009 users of DMPA were at increased risk of developing an abnormally low HDL level as well as an abnormally high LDL level and an increase in the LDL: HDL cholesterol ratio, although these effects appeared to be temporary (Berenson *et al*., 2009). All currently used synthetic progestogens decrease circulating levels of HDL, which is one of the key metabolic changes that can be linked to an increase in the incidence and severity of cardiovascular disease, particularly ischemic heart disease (Kremer *et al*., 1980, Miller *et al*.,1981.). However Tikkanen *et al*., 1981 suggested that this decline in HDL is associated more with androgenic progestins.

### Castelli Index (Cholesterol Ratio)

The associations of total cholesterol and the proportion of cholesterol in individual lipoprotein classes to coronary heart disease are complex. To help simplify these relationships, cholesterol values are often combined into one summary estimate to form a single risk factor with a relationship to disease that is more easily described. Castelli *et al*., 1983 investigated the ratio of total cholesterol to high-density lipoprotein cholesterol (Castelli index I) and the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol (Castelli index II) as these ration are found to be the strong predictors of coronary heart disease. It is now generally accepted that both elevated levels of non-high-density lipoprotein cholesterol and low HDL-C concentrations may promote the development of atherosclerosis. This is supported by data from the Framingham study,1 which showed that as the ratio of total cholesterol:HDL-C increases, so does the risk of coronary heart disease (CHD). In populations with low CHD incidences, average values of Total-C/HDL-C are below 4.0 ( Kannel *et al*., 1987).

## MATERIALS AND METHODS

The study was carried out in family planning departments of different clinical setting in Karachi. Young females maintained on any type of contraceptives for at least one year were randomly invited and reviewed for their complete medical and family history. Informal verbal consent had taken and blood samples of 54 women who responded and agreed to participate in the research were collected.

Participants were divided into 4 groups:
1. Women on oral contraceptives.
2. Women on injectables. (DMPA ,NET-EN )
3. Women on subdermal implants.
4. Women on IUCDs
5. The chemical composition of the contraceptives used in this study is as follows

➢ OC: 0.3 mg norgestrol+0.03mg ethinyl estradiol+75 mg ferrous sulphate.
➢ DMPA: Depomedroxy progesterone acetate 150mg/ml.
➢ NET-EN: Norethisterone enantate 200 mg/ml.
➢ Implant: 36 mg of levonorgesterol.
➢ Cu-T: non hormonal T –shaped contraceptive device containing copper.

Fasting blood sample of about 7 ml were collected from these subjects to perform lipid profile on chemistry analyzer, Humalyzer 3000 (Human Germany) using standard kits. The data was collected on a predesigned performa, and was also entered on Microsoft Excel.

All the values were expressed as the means and standard error to the mean (S.E.M) and analyzed by calculating Castelli indices I & II and percentile differences among different contraceptive groups.

**Table. 1:** Effects of Contraceptives on Lipid Profiles.

| Parameters | Reference ranges (mg/dl) | Type of contraception / no. of subjects in each group | | | | |
|---|---|---|---|---|---|---|
| | | IUCD group N= 6 | Implant group N= 4 | NET-EN group N=18 | DMPA group N=14 | OC group N=12 |
| Total Cholesterol | <200 | 148.3±15.65 | 135.2±6.435 | 147.8±6.435 | 144.5±7.947 | 162.2±10.456 |
| Triglycerides | <200 | 110±11.80 | 73.25±12.42 | 103.22±10.34 | 92.07±9.489 | 94.67±10.28 |
| HDL | >35 | 36.83±0.792 | 34.25±1.931 | 36.778±1.238 | 37.357±0.970 | 37.417±0.773 |
| LDL | <190 | 89.50±16.57 | 86.25±3.09 | 93.72±4.896 | 88.79 ±7.444 | 105.92±8.640 |

**Table. 2:** Percentile Differences of Lipid Profiles in Different Contraceptive Groups.

| Contraceptive Compared | Total Cholesterol | Triglycerides | HDL | LDL |
|---|---|---|---|---|
| IUCD – IMPLANT | 8.83 | 33.3 | -7 | -3.63 |
| IUCD –NET-EN | 0.33 | 6.78 | 0.13 | -4.48 |
| IUCD-DMPA | 2.62 | 19.6 | -1.41 | -0.78 |
| IUCD-OC | -8.56 | -16.36 | -1.57 | -15.48 |
| IMPLANT-NET-EN | -8.52 | -28.9 | -6.87 | -7.95 |
| IMPLANT – DMPA | -6.43 | -20.4 | -8.32 | -2.87 |
| IMPLANT-OC | -16.64 | -22.59 | -8.47 | -18.55 |
| NET-EN – DMPA | 2.23 | 10.7 | -1.57 | 5.22 |
| NET-EN –OC | -8.87 | -8.97 | -1.71 | -11.52 |
| DMPA-OC | -10.9 | -2.74 | -0.16 | -16.1 |

## RESULTS

Table 1 reveals the mean concentration of lipid parameters of different groups of contraceptive users. All the values are expressed in terms of mean ± S.E.M. The serum concentrations of total cholesterol, triglycerides, HDL and LDL in all groups lies fairly within reference ranges with the exception of Implant which showed the decreased levels of HDL with the value of 34.25±1.931 mg/dl.

Table 2 reveals the comparisons of lipid profiles of different contraceptive users. All the values are expressed in terms of percentile differences of mean. Negative values indicate the comparitive decline in the levels of parameters analyzed.

Fig: 1 & 2 revealed the Castelli indices I (total cholesterol/HDL) and II (LDL/HDL). It is apparent from the results that Castelli index I was found to exceed its optimal reference ranges in certain contraceptive groups. OC poses highest ratio of 4.313±0.225 and DMPA poses the lowest ratio of 3.866±0.188 while NET-EN, IUCD and Implant revealed the ratio of 4.009±0.0837, 4.004±0.360 and 3.950±0.051 respectively. Castelli index II is found to lie in normal reference range in different contraceptive groups but still found to be touching the cut off range with the values as high as 2.828±0.1963 to as low as 2.379±0.1867 as in Fig.2
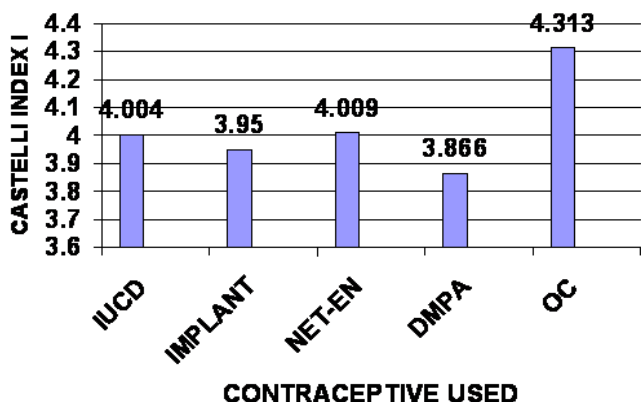


**Fig. 1:** Castelli Indices 1 (Total cholesterol- HDL ratio) of Contraceptives Studied.
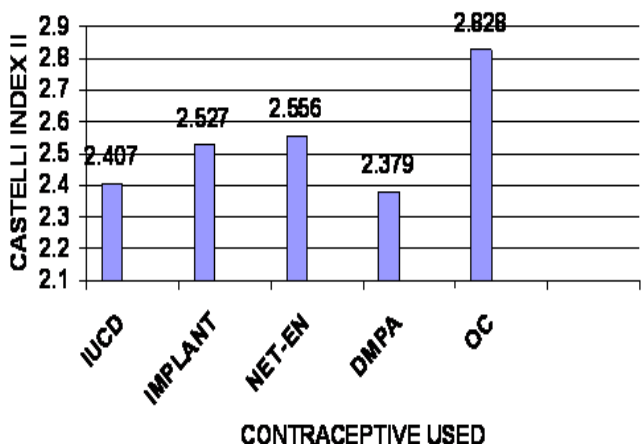


**Fig. 2:** Castelli indices II (LDL-HDL ratio) of Contraceptives studied.

## DISCUSSION

Serum **total cholesterol** level is a major indicator of risk of coronary heart disease; for every 1% increase in the total serum cholesterol level, a 2% increase in incidence of coronary heart disease is found (Castelli et al., 1998). Oral contraceptive use may be associated with an enhanced rise in total cholesterol during adolescence (Tim et al., 2003, Van et al., 1990). DMPA users have reported significantly higher Total cholesterol when compared with OCs and Implant (Diab et al., 200). Implant use has shown to decrease total cholesterol levels in certain studies (Suharti et al., 1999). However in present study the total cholesterol levels were found to be highest in the OC group and lowest in the implant group, while IUCD, NET-EN and DMPA lies in between two extremes in continuation with the previous studies. OC use is associated with 16.64%, 10.9%, 8.87% and 8.56 % high total cholesterol levels as compared to Implant, DMPA, NET-EN and IUCD use respectively.

A high level of **low-density** lipoproteins is an independent risk factor for coronary heart diseases in both men and women (Castelli et al., 1998). Excessive influx of LDL cholesterol by way of the "scavenger pathway" may result in deposition of cholesterol in arterial walls and atheroma formation (Tikkanen et al., 1990). Currently used lower doses of OCs have mild adverse effect on the lipid profile as they cause little increase in LDL and a variable but smaller decrease in HDL (Thorogood et al., 1993). Although in general, the lipoprotein changes were greater in magnitude with higher dose oral contraceptive preparations, they can be significant in lower dose preparations as well since the oral contraceptive preparation tend to increase LDL levels in various studies (Krauss et al., 1992). Injectable contraceptives on the other hand have the capability of increasing LDL cholesterol (Berenson et al., 2009, Enk et al., 1992). Though this increment of LDL by injectable contraceptives have been shown to be transiet and revert back after 6 months of use in some studies (Berenson et al., 2009). The use of hormonal implants is associated with either no change or slightly decreases in LDL levels (Araujo et al., 2006). Comparison of LDL levels in the present study showed the results in continuation with the previous results in the way that OC group showed the highest levels of LDL whereas Implant was on the other end with lowest levels. Furthermore NET-EN, IUCD and DMPA showed the LDL levels in between these two extremes. Starting with the highest LDL level, OC use was found to be associated with 18.55%, 16.1%, 15.48% and 11.52% high LDL levels as compared to Implant, DMPA, IUCD and NET-EN respectively. So it can be evident that OC group poses the highest atherogenic potential followed by NET-EN, IUCD, DMPA and implant respectively.

High **triglyceride** level is an independent risk factor only in women (Castelli et al., 1998). The triglycerides are less related to cardiovascular risk and only gain importance when associated with other lipid abnormalities, such as low HDL cholesterol or high cholesterol (Castelli et al., 1998). Combination OC use increase plasma triglycerides (Tikkanen et al., 1990). However in contrast

to endogenous hypertriglyceridemia, an EE-induced rise in triglyceride levels does not appear to increase cardiovascular risk if LDL is not increased (Enk *et al*., 1992). NET-EN use has reported to have no effect on serum triglycerides (Araujo *et al*., 2006). However Kandeel, *et al*., 1984 reported to have decrease in triglycerides levels with NET-EN use (Weigratz *et al*., 1998). Similar to NET-EN DMPA use is also not associated with any change in triglyceride levels (Fotherby *et al*., 1982). Implant seems to reduce the hepatic secretion of lipoproteins and produce reduction in cholesterol, HDL, and triglycerides (Kandeel *et al*., 1984). When different contraceptives were compared in present study it is noted that non-hormonal IUCD use is associated with highest triglycerides levels followed by NET-EN, OCs, DMPA and lastly Implant.

In contrast to all other lipid parameters, the higher the level of high-density lipoprotein, the lower the risk of coronary heart disease by increasing cholesterol transport to the liver, where it is cleared through a process called reverse transport (Castelli *et al*., 1998). Estrogens tend to increase the levels of HDL (Krauss *et al*., 1992) and for the same reason users of OCs experienced significantly greater increases in HDL levels than did non hormonal-contraceptive users (Berenson *et al*., 2009). Injectable contraceptives including NET-EN and DMPA have shown to decrease HDL cholesterol (Kremer *et al*., 1980, WHO *et al*., 1986). However this decline in HDL is associated with androgenecity of the progestins (Tikkanen *et al*., 1981) Studies indicate no change or a small decline in the HDL cholesterol levels of Implant users whereas Araujo *et al*., 2006 reported the drastic decline of HDL to about 28.9% after 5 years of Implant use in his study. However in present study Implant in comparison to other contraceptive groups showed lowest levels of HDL which is in continuation with Araujo *et al*., 2006. OC group on the other hand showed the highest HDL levels compared to other contraceptive groups which is suggestive of estrogenic effect of oral contraceptives. Implant group showed the difference of 7%, 6.87%, 8.32% and 8.47% low HDL levels as compared to IUCD, NET-EN, DMPA and OC respectively. In contrast to previous studies injectable contraceptives did not show any drastic decline in HDL levels.

Collectively evaluation of lipid profiles in the present study suggested that on comparison to other contraceptive groups OCs use showed the association of high LDL, HDL and total cholesterol levels, the LDL levels were found to be 11.5 %, 16.15% and 18.55 % high in comparison with NET-EN, DMPA and Implants respectively which are progesterone only methods. However HDL levels in OC, DMPA, NET-EN and IUCD groups were found to lie in normal ranges, where as Implants showed the decreased HDL levels. Triglycerides levels were highest in IUCD users followed by NET-EN, OC, DMPA and Implants respectively.

The Castelli indices I and II were also measured to evaluate the risk of CVD. The **Castelli index I** (Total cholesterol/HDL) that should be <4 for normal subjects was found to be ranging from 3.866 to 4.313, where OCs showed the highest

ratio (4.313) and DMPA showed the lowest total cholesterol/HDL ratio (3.86) whereas NET-EN, IUCD and Implant lie in between these two extremes with the ratio of 4.009, 4.004 and 3.95 respectively.

Castelli index II (LDL/HDL) was found to be very close to the upper limit of the normal range (<3). It ranges from 2.37 to 2.82, where OCs showed the highest and DMPA showed the lowest value with IUCD, Implants and NET-EN lying in between these two.

On analyzing this data on the recommendations of ATP III, National Heart and Lung Institute (NCEP *et al*., 2009) for risk level of CVD it is quite clear that the use of all contraceptives poses low-average risk, of which OC poses the highest risk followed by NET-EN, IUCD, Implant and DMPA. As this risk level is not drastically different between hormonal and non-hormonal method it is difficult to point out hormonal content of contraceptive methods responsible for this change. This risk may be attributable to other life style factors including lack of exercises and increased intake of cholesterol rich diets but still the hormonal factor cannot be excluded in manipulating the CVD risk. Furthermore, it should also be mentioned that this study was conducted in clinical settings where contraceptives are prescribed after having complete general and medical histories of the females under close monitoring. Hence their use would be discontinued with the appearance of any symptoms of their side effects within few months of its initiation. Therefore it is one of the reasons that results of present study shows minimal risk. It should be noted that the present study was conducted in females well maintained on these contraceptives and females vulnerable to the risks were excluded from the study as they have very less period of hormonal contraceptive use. It should also be mentioned that this study group comprised of young females with the age ranging from 26±2.5 to 32.2±6.24 years and this young group showed the predisposition to sub clinical cardiovascular risk on contraceptive use and thus it should not be overlooked that continuation of hormonal method till menopause may change this slight predisposition to well-defined clinical cardiovascular disease later in their lives.

## CONCLUSION

It is therefore suggested that hormonal contraception should be used under close monitoring until further studies would be conducted to completely eradicate the risk associated with hormonal preparations and over the counter use of hormonal contraceptive should be discouraged which is a very common practice in our population.

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