Biochemical Effects of Oral Contraceptives among Users: A Review

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Abstract: Oral contraceptives (OC) are widely used to prevent ovulation, implantation and therefore pregnancy. The widespread use of the oral contraceptive pills provides an opportunity for assessing their influence on various biochemical parameters i.e., enzymatic, serum lipid and proteins among users. Recent studies have shown its implication in many diseases such as thromboembolic disease, myocardial infarction, circulatory disorders and carcinogenicity. The negative effects on the liver and heart have also been reported due to high serum cholesterol levels among OC for their possible biochemical effects.

Key words: Oral contraceptives pills, biochemical studies, oral contraceptive users

INTRODUCTION

By the early twentieth century, scientists were eager to isolate and wanted to determine the formulation and structural properties of synthetic hormones and they found that the high doses of these synthetic hormones inhibited ovulation. The synthetic progesterone compounds that are used as an oral contraceptives are Norethisterone and Norethynodrel. These compounds were first tested in woman in 1956 in the United States, Puerto Rico and Haiti. The first pill that was launched as an oral contraceptive for use contains the combination of nor-19 progestin with a small amount of synthetic estrogen as a trade name Enovid (Jumod and Marks, 2002). Now-a-days million of women of reproductive age around the world use oral contraceptives (Burkman, 2001). Over the decades, the use of oral contraceptive pills is increasing in India (Sharma et al., 2001). In recent years, it is reported that the use of oral contraceptive pills by women is increasing as the government and various organizations are campaigning for its use in order to avoid pregnancies especially in developing countries like Nigeria (Emokpaa et al., 2010). According to Bukvic et al. (2000) oral contraceptives pills that are synthesized chemically can be carcinogenic. For avoiding unwanted pregnancy the combined oral contraceptives should be taken by users that consist of the steroid hormone estrogens in combination with a progestogen (IARC, 1979, IARC, WGESRCH and WHO, 1987). They are currently available in monophasic, biphasic and triphasic preparations, depending on the number of different doses of progestogen. Monophasic pills maintain a constant dose of estrogens and progestogen, while multiphasic pills allow a lower total dose of progestogen to be given by reducing the amount of progestogen early in the 20-22 day period of exposure. Progestin-only contraception is an option for women that contain only progestin. The most common side-effects of progestin only contraception is complication in pregnancy or ecysis and irregularity in menstrual cycle. Oral contraceptives have been shown abrupt increase in the risk of non-fetal myocardial infarction (Ory, 1977; Mann et al., 1975). Both single progestins and combined oral contraceptive shows the genotoxic damage and risk of cancers. Study stated that steroids shows genotoxic damage at higher doses (Siddique et al., 2006, 2005; Siddique and Afzal, 2004). The therapeutic doses are safe, but care should be taken with regard to their concentration as they may be genotoxic in the long term use in humans (Siddique and Afzal, 2008; Siddique et al., 2007; Siddique and Afzal, 2005). The International Agency for Research on Cancer (IARC) concluded that progestins (progestogens) are very much prone to carcinogenic to humans. This risk is probably due to hormonal steroids, since these steroids are very much carcinogenic to humans (Brambilla and Martelli, 2002). The present review gives a brief account of the studies carried out on the biochemical effects of oral contraceptives among users.

Biochemical effects: Estrogen increases the serum High Density Lipoprotein Cholesterol (HDL-C) levels and decrease the levels of Low-density Lipoprotein Cholesterol (LDLC), whereas progestogens have a reverse effect i.e., they reduce High-density Lipoprotein Cholesterol (HDL-C) and raise Low-density Lipoprotein

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Cholesterol (LDLC) levels. The lipoprotein profile, resulting from the use of oral contraceptives is therefore, dependent on the balance between the potencies of the estrogen and progestogen components. Although, the high-dose progestogens contained in the older oral contraceptives did raise Low-density Lipoprotein Cholesterol (LDLC) and reduce High Density Lipoprotein Cholesterol level (HDLC), modern low-dose progestogens do not appear to affect the lipid profile in users. The increased risk of cardiovascular disease in oral contraceptive users is due to venous or arterial thrombosis (Speroff and Darney, 1996; Brennan et al., 1997).

Several studies have been performed on the biochemical effect among oral contraceptives users. Several authors have observed that the use of oral contraceptive pills (OCPs) may increase the risk of cardiovascular disease by increasing the levels of triglycerides (WHO, 1995), but the position over the cholesterol is not clear. Wynn et al. (1966) have reported a significant difference in cholesterol levels in young women using OCP. Other authors observed a significant increase in all lipid fractions in women using OCPs (Donde and Virkar, 1975). Another study showed that serum total cholesterol levels were higher among oral contraceptive users. There was an increase in total cholesterol due to the increased in β-lipoprotein cholesterol. A decrease in α-lipoprotein cholesterol and an increase in triglycerides was also observed (Webber et al., 1982). Over the 3 years of study duration, OC users experienced an increase in the levels of triglycerides, total cholesterol, VLDL and HDL that were greater than those experienced by non-hormonal contraceptive users (Berenson et al., 2009). One of the long-range potential concerns with the use of Oral Contraceptive Agents (OCA) is the increase in serum lipids. Women in the OCA group have significantly higher triglyceride levels than women in the non OCAs group (Smith et al., 1975).

In a study on Nigerian oral contraceptive users the level of serum cholesterol was significantly higher as compared to controls. The elevation of serum cholesterol level may be due to the estrogen content in oral contraceptives. In conclusion, this study has demonstrated the need to periodically reassess the biochemical parameters of oral contraceptive users, especially those who have been on the steroids for a long time. This is necessary in view of the subtle but significant biochemical changes as regards increases of total protein, albumin and cholesterol levels (Obisasan et al., 2002). Another study on biochemical changes on oral contraceptive have shown the higher levels of triglycerides, total cholesterol, LDL-cholesterol and VLDL-cholesterol in OC users women. The increase in OCP triglycerides is due to the increase in the synthesis. OCP intake produce changes in lipid metabolism in women, but such changes may not necessarily lead to pathogenic concentration resulting in a cardiovascular disease with the prolonged use of not more than 4 years (Emokpae et al., 2010). Since, the effects caused by OCP intake are short lived, it could be said that the effects of these hormonal preparations may be physiologic rather than pathogenic (Karam, 2001).

Many studies have analyzed the relation between cardiovascular risk factors and oral contraceptive use in adult women. Elevated blood levels of lipids are probably the most important biochemical risk factor for atherosclerosis. In the liver triglycerides synthesis is enhanced by estrogen and inhibited by androgen and these triglycerides are partly brought into the circulation as low-density lipoproteins. In another study it was observed that in adolescent girls serum total cholesterol was significantly higher among oral contraceptive users compared to non-users (Nawrot et al., 2003).

The effects of Oral Contraceptive Agents (OCAs) on lipid metabolism were reviewed recently by Beck (1973) who points out that the estrogen-induced rise in serum triglyceride levels is dose regulated and is similar to the general increase in serum triglycerides found in postmenopausal women. Oral contraceptives have been reported to affect all serum lipids, but their effect on the triglycerides and VLDL is most consistent and striking (Gershberg et al., 1968; Molitch et al., 1974). Some data also showed a small, non significant inverse relationship between OC users and HDL cholesterol. A recent report showed that different OC preparations had varying effects on HDL cholesterol. HDL cholesterol levels appeared to be directly related to estrogen dose and inversely related to progestin dose (Bradley et al., 1978).

**Mechanism of action of oral contraceptives**

**Combination oral contraceptives**: Combination oral contraceptives are the most widely used oral contraceptives, that prevents pregnancy mainly by suppressing ovulation. Both progestogen and estrogen components suppress luteinizing hormone secretion, which prevents ovulation. In addition, progestogen thickens cervical mucus so that sperm cannot penetrate the uterus and produces an endometrium that is unreceptive to ovum implantation. It may also contribute to contraception by interfering with secretary and peristaltic functions inside the fallopian tube (Hatcher et al., 1994). Estrogens and progestogens suppress the secretion of follicle-stimulating hormone,
which prevents the selection and emergence of a dominant follicle. They also minimize breakthrough bleeding by stabilizing the endometrium so that irregular shedding is prevented. Because the estrogen component potentiates the contraceptive action of the progesterone component (probably by increasing the level of intracellular progesterone receptors), only a minimal dose of estrogen is needed to maintain the efficacy of the combination oral contraceptive (Speroff and Darney, 1996).

**Progestin-only oral contraceptives:** As the progestogens themselves do not always suppress gonadotropins, women who take progestin-only oral contraceptives do not always ovulate. The contraceptive efficacy of the progestin-only oral contraceptive is therefore dependent mostly on its effects on cervical mucus, on the endometrium and possibly also on the fallopian tube (Speroff and Darney, 1996). The progestin-only minipill must be taken every day at the same time because its circulating progestogen level is about 75% lower than the level resulting from a combination oral contraceptive. Use of the minipill may result in irregular menstrual bleeding and the development of functional ovarian follicular cysts. Minipills containing levonorgestrel have been associated with acne. The acne is caused by the androgenic activity of the unopposed progestogen, despite its very low dose, which decreases the level of circulating sex hormone binding globulin. As a result, biologically available levels of levonorgestrel and testosterone are increased. Low-dose combination oral contraceptives do not produce acne because estrogen, which increases sex hormone binding globulin, counteracts the effect of progestogen (Speroff and Darney, 1996). The minipill does not significantly affect lipid levels, carbohydrate metabolism, or blood coagulation. When it is discontinued, fertility returns promptly (Hatcher et al., 1994).

Studies carried out on the biochemical effects on oral contraceptives are as given in Table 1.

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## CONCLUSION

The studies performed on Oral contraceptive users clearly shows the marked effects on enzymes, carbohydrates and serum lipids. High level of serum lipid invites many problems to the contraceptive users i.e., cardiovascular risk by increase in the cholesterol level but the full impact of oral contraceptive on cardiovascular risk factors may not be fully concluded from the short duration of studies done so far. The duration of oral contraceptive also have importance in studying the effect among the women. We must learn the correct duration of usage/dosage more wisely and keep their user aware about the affect of oral contraceptive. The efforts should continued to produce safer oral contraceptive for the users.

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