International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 8 (5): 314-320, 2012
ISSN 1811-7775 / DOI: 10.3923/ijp.2012.314.320

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 Enovoid (Junod 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 (Emokpae *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, WGECRH 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 eccysis 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 (HDLC) levels and decrease the levels of Low-density Lipoprotein Cholesterol (LDLC), where as progestogens have a reverse effect i.e., they reduce High-density Lipoprotein Cholesterol (HDLC) and raise Low-density Lipoprotein

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Cholesterol (LDLC) levels. The lipoprotein profile, resulting from the use of oral contraceptive 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 (Obisesan *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 OCs 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 secretory 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 progestogen component (probably by increasing the level of intracellular progestogen 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.

Table 1: Studies on biochemical effects of oral contraceptives

Oral contraceptive	Parameter studied	Conclusion	Author
Estrogen containing oral contraceptive	Blood pressure and serum lipids	Higher level of serum lipid and lower blood pressure	Webber *et al*. (1982)
Oral pill (Triphasic OC), Vaginal ring (NuvaRing), Transdermal patch (Ortho Evra)	Lipid soluble Antioxidant and Serum levels of enzyme	Low lipid serum level, decrease coenzyme θ_{10} and total anti-oxidant capacity Assay	Palan *et al*. (2010)
Injectable (DMPA-depot medroxyprogesterone acetate), Oral pill-ethinyl estradiol and desogestrel	Serum lipids	Elevate lipid level in oral pill users and low HDL and high LDL level in DMPA users	Berenson *et al*. (2009)
Oral contraceptives	Serum protein and cholesterol	Higher serum protein, increased cholesterol levels	Obisesan *et al*. (2002)
Low dose contraceptives (ethinylestradiol) combined with progestin component dienogest or drospirenone	Effect on deep venous thrombosis and arterial by lipid abnormalities	Deep venous thrombosis in users (arterial thrombosis increases)	Tzankova *et al*. (2010)
Biphasic lofeminal tablets (norgestrel+ ethinylestradiol)	Serum lipids and blood pressure	Total lipid increases reduced blood pressure level	Emokpae *et al*. (2010)
Ethinylestradiol and progestin	Blood pressure and Serum total lipids	Higher systolic blood pressure and higher level of serum total lipids	Nawrot *et al*. (2003)
Low dose oral contraceptive (ethinyl estradiol/gestodene)	Lipid level and Blood pressure	Normal level of lipids, Normal blood pressure	Giribela *et al*. (2007)
Monophasic pills (ethinyl estradiol)	Blood sample (Total plasma cortisol was measured with a radioimmunoassay) and first saliva sample (Basal free cortisol level)	Basal free cortisol level increases, No effect on cortisol level	Kirschbaum *et al*. (1999)
Combined oral contraceptive (estrogen ethinylestradiol+progestogen)	Serum Lipids and lipoproteins	Serum lipids is higher	Abdel-Barry *et al*. (2011)
Lyndiol pill (lynoestrenol and progestin)	SGOT levels (serum glutamic oxaloacetic transaminase)	Increase in SGOT (serum glutamic oxaloacetic transaminase)	Stoll (1967)
Oral contraceptive agents combination type (Progestogen+Estrogen)	Concentration of plasma ascorbic acid in leukocytes	Decrease plasma ascorbic acid	McLeroy and Schendel (1973)
Norinyl (1 mg of norethindrone +80 μg of mestranol).	Vitamin level and lipid levels in serum	Decrease in serum vitamin B12, Lipid level in serum higher	Smith *et al*. (1975)
Oral contraceptive	Serum lipids	Increase level of serum lipids	Kannel (1979)
Oral contraceptive pill (norethindrone+ mestranol)	Serum lipids	Higher levels of total lipids	Hennekens *et al*. (1979)
Contraceptive pill (levonorgestrel+ ethinylestradiol)	Serum lipids	Decrease serum lipids	Demacker *et al*. (1982)
Contraceptive pill	Plasma vitamins (A, E, C) plasma triglycerides and cholesterol, leukocytes	Increase level of vitamin, plasma, triglycerides, cholesterol, leukocytes that makes the risk of myocardial infection	Yeung (1976)

Table 1: Continue

Oral Contraceptive	Parameter Studied	Conclusion	Author
Norethindrone, Ortho-Novum (1/35 and 777), ethynodiol diacetate	Lipoproteins and Serum lipids.	Higher lipoprotein, high Serum lipids	Walsh and Sacks (1993)
Combined oral contraceptive estrogen+progestin(desogestrel, levonorgestrel and norethisterone)	Histopathology	Risk of endometrial cancer is decreased	Weiderpass *et al*. (1999)
Combined pills (ethinylestradiol)	Bone markers, Serum biochemistry, Bone mineral measurement	Decreased bone formation; serum albumin is lower in oral contraceptive users. Normal bone mineral	Garnero *et al*. (1995)
Oral contraceptive pill	Serum levels of lipid-soluble antioxidants	Lower level of serum levels of lipid soluble antioxidants	Palan *et al*. (2006)
Levonorgestrel (90 μg), ethinyl estradiol (20 μg)	Demographic data	Use of this composition does not delay the return to fertility	Barnhart *et al*. (2009)
Monophasic oral contraceptive (levonorgestrel (100 μg) +ethinylestradiol 20 μg)	Follicle diameters and serum progesterone and 17 β-estradiol	Suppression of ovarian activity in users	Coney and DelConte (1999)
Ortho-Novum 7/7/7, Triphasil (combination of Norethindrone, ethinyl estradiol),	Serum concentration of ethinylestradiol by Radioimmunoassay	Serum concentration of ethinylestradiol increases	Sinofsky and Pasquale (1998)
Cyproterone acetate, Lipid metabolism, hirsutism +ethinylestradiol Desogestrel+ethinyl estradiol	Lipid metabolism increased, of adolescents with polycystic ovary syndrome (PCOS)	Lipid metabolism increased, decrease hirsutism	Mastorakos *et al*. (2002)
Mifepristone (contraceptive pill)	Biochemical parameter (serum alkaline phosphatase and serum glutamyl pyruvate transaminase)	Increase biochemical parameters (serum alkaline phosphatase and pyruvate transaminase), serum glutamyl	Agarwal *et al*. (2009)
Ethinylestradiol and chlormadinone acetate	Assessment of ovarian function, thickness of endometrium, cervical reaction sex, hormone level and overall tolerability	Inhibition of ovulation and unfavourable condition for fertilization, pregnancy	Spona *et al*. (2010)
Depot medroxyprogesterone Oral contraceptive pill (20 μg),	Menstrual symptoms and Physiologic symptoms	No adverse effects	Berenson *et al*. (2008)
Oral contraceptive (ethinyl estradiol+ norgestimate) Contraceptive patch (ethinylestradiol+norelgestromin)	Body Mass Index (BMI) and serum androgen levels	The contraceptive patch had an effect comparable, to the OC on several key androgenic potential as a therapeutic agent for disorders of androgen excess	White *et al*. (2005)
Ethinylestradiol+progestin	Pelvic pain, bleeding, headaches, breast tenderness	Pelvic pain, bleeding and breast tenderness shown, headaches problem, breast tenderness shown	Sulak *et al*. (2000)
Oral contraceptive (estrogen), DMPA(progestin)	Demographic data form, serum testosterone and estradiol level	Oral contraceptives have low level of testosterone compared to DMPA and high level of estradiol	Schaffir *et al*. (2010)
Oral contraceptive (30 μg ethinyl estradiol+2 mg dienogest)	Survey based Study	Slight delay in regaining fertility after the use of this oral contraceptive.	Wiegratz *et al*. (2006)
Mircette (desogestrel/ethinyl estradiol)	Serum lipids, carbohydrate metabolism, endocrine parameters	Increase serum lipids, no changes in carbohydrate metabolism, effect on endocrine parameter	Berga (1998)
Oral contraceptive Pill	Standard questionnaire was used to record descriptive characteristics and medical and reproductive history	Liver carcinoma found in oral contraceptive users	Palmer *et al*. (1989)

CONCLUSION

The studies perform 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.

ACKNOWLEDGMENT

The authors are thankful to University Grant Commission (UGC), New Delhi for the award of project entitled: Biochemical and Cytogenetic effects of Oral Contraceptives among women of different reproductive histories {F.No. 39-582/2010(SR)} to Dr. Yasir Hasan Siddique, Department of Zoology, Aligarh Muslim University, Aligarh.

REFERENCES

Abdel-Barry, J.A., M.S. Flafl, L.M. Al-Namaa and N.A. Hassan, 2011. Lipoprotein changes in women taking low-dose combined oral contraceptive pills: A cross-sectional study in Basra, Iraq. East. Mediterr. Health J., 17: 684-688.

Agarwal, M., V. Das, A. Agarwal, A. Pandey and D. Srivastava, 2009. Evaluation of mifepristone as a once a month contraceptive pill. Am. J. Obstet. Gynecol., 200: e27-e29.

Barnhart, K., S. Mirkin, G. Grubb and G. Constantine, 2009. Return to fertility after cessation of a continuous oral contraceptive. Fertil. Steril., 91: 1654-1656.

Beck, P., 1973. Contraceptive steroids: modifications of carbohydrate and lipid metabolism. Metabolism, 22: 841-855.

Berenson, A.B., M. Rahman and G. Wilkinson, 2009. Effect of injectable and oral contraceptives on serum lipids. Obstet. Gynecol., 114: 786-794.

Berenson, A.B., S.D. Odom, C.R. Breitkopf and M. Rahman, 2008. Physiologic and psychologic symptoms associated with use of injectable contraception and 20 μg oral contraceptive pills. Am. J. Obstet. Gynecol., 199: 351.e1-351.e12.

Berga, S.L., 1998. Metabolic and endocrine effects of the desogestrel-containing oral contraceptive mircette. Am. J. Obstet. Gynecol., 179: S9-S17.

Bradley, D.D., J. Wingerd, D.B. Petitti, R.M Krauss and S. Ramcharan, 1978. Serum high-density-lipoprotein cholesterol in women using oral contraceptives, estrogens and progestins. N Engl. J. Med., 299: 17-20.

Brambilla, G. and M. Martelli, 2002. Are some progestins genotoxic liver carcinogens? Mutat. Res., 512: 155-163.

Brennan, P., C. Bankhead, A. Silman and D. Symmons, 1997. Oral contraceptives and rheumatoid arthritis: Results from a primary care-based incident case-control study. Semin. Arthritis Rheum., 26: 817-823.

Bukvic. N., F. Susca, D. Bukvic, M. Fanelli and G. Guanti, 2000. 7-α-ethinylestradiol and norgestrel in combination induce micronucleus increases and aneuploidy in human lymphocyte and fibroblast cultures. Teratogenesis Carcinog. Mutagen., 20: 147-159.

Burkman, R.T., 2001. Current perspectives on OCs. Dialogues Contraception, 6: 15-17.

Coney. P. and A. DelConte, 1999. The effects on ovarian activity of a monophasic oral contraceptive with 100 μg levonorgestrel and 20 μg ethinyl estradiol. Am. J. Obstet. Gynecol., 181: S53-S58.

Demacker, P.N., R.W. Schade, A.F. Stalenhoef, P.M. Stuyt and A. van't Laar, 1982. Influence of contraceptive pill and menstrual cycle on serum lipids and high-density lipoprotein cholesterol concentrations. Br. Med. J., 284: 1213-1215.

Donde U.M. and K. Virkar, 1975. Effect of contraceptive steroids on serum lipids. Am. J. Obstet. Gynecol., 123: 736-741.

Emokpae, M.A., P.O. Uadia and H.B. Osadolar, 2010. Effect of duration of use of hormonal contraceptive pills on total lipid and lipoproteins in Nigerian women. Int. J. Pharm. Bio. Sci., 1: 1-5.

Garnero, P., E. Sornay-Rendu and P.D. Delmas, 1995. Decreased bone turnover in oral contraceptive users. Bone, 16: 499-503.

Gershberg, H., M. Hulse and Z. Janvier, 1968. Hypertriglyceridemia during treatment with estrogen and oral contraceptives: An alteration in hepatic function? Obstet. Gynecol., 31: 186-189.

Giribela, C.R.., M.C. Rubira, N.R. Melo, R.D. Plentz, K. Angelis, H. Moreno and F.M. Consolim-Colombo, 2007. Effect of a low dose oral contraceptive on venous endothelial function in healthy young women: Preliminary results. Clinics, 62: 151-158.

Hatcher, R.A., J. Trussel and F. Stewart, 1994. Contraception Technology. 16th Edn., Irvington Publishers, New York.

Hennekens, C.H., D.A. Evans, W.P. Castelli, J.O. Taylor, B. Rosner and E.H. Kass, 1979. Oral contraceptive use and fasting triglyceride, plasma cholesterol and HDL cholesterol. Circulation, 60: 486-489.

IARC, 1979. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Sex Hormones (II) Lyon., 21: 105-106.

IARC, WGECRH and WHO, 1987. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. In: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs, IARC, (Eds.). Vol. 1-42, International Agency for Research on Cancer, Lyon, France, pp: 272-310.

Junod, S.W. and L. Marks, 2002. Women's trials: The approval of the first oral contraceptive pill in the United States and Great Britain. J. Hist. Med. Allied Sci., 57: 117-160.

Kannel, W.B., 1979. Possible hazards of oral contraceptive use. Circulation, 60: 490-491.

Karam, J.A., 2001. The Gonadal Hormones and Inhibitors. Basic and Clinical Pharmacology. 8th Edn., Appleton and Lange Publishers, USA., ISBN: 0-8385-0592-9, pp: 679-708.

Kirschbaum, C., B.M. Kudielka, J. Gaab, N.C. Schommer and D.H. Hellhammer, 1999. Impact of gender, menstrual cycle phase and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom. Med., 61: 154-162.

Mann, J.I., M.P. Vessey, M. Thorogood and S.R. Doll, 1975. Myocardial infraction in young women with special reference to oral contraceptive practice. Br. Med. J., 2: 241-245.

Mastorakos, G., C. Koliopoulos and G. Creatsas, 2002. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertil. Steril., 77: 919-927.

McLeroy, V.J. and H.E. Schendel, 1973. Influence of Oral contraceptive on ascorbic acid concentration on healthy, sexually mature women. Am. J. Clin. Nutr., 26: 191-196.

Molitch, M.E., P. Oill and W.D. Odell, 1974. Massive hyperlipemia during estrogen therapy. J. Am. Med. Ass., 227: 522-555.

Nawrot, T.S., E.D. Hond, R.H. Fagard, K. Hoppenbrouwers and J.A. Staessen, 2003. Blood pressure, serum total cholesterol and contraceptive pill use in 17-year-old girls. Eur. J. Cardiovasc. Prevention Rehab., 10: 438-442.

Obisesan, K.A., F.A. Adenaike, M.A. Okunlola and A.A. Adenaike, 2002. Effects of oral contraceptives on total serum proteins, albumin, globulins and cholesterol levels in Ibadan, Nigeria. West Afr. J. Med., 21: 197-199.

Ory, H.W., 1977. Association between oral contraceptives and myocardial infarction: A review. J. Am. Med. Ass., 237: 2619-2622.

Palan, P.R., A.T. Magneson, M. Castillo, J. Dunne and M.S. Mikhail, 2006. Effects of menstrual cycle and oral contraceptive use on serum levels of lipid-soluble antioxidants. Am. J. Obstet. Gynecol., 194: e35-e38.

Palan, P.R., F. Strube, J. Letko, A. Sadikovic and M.S. Mikhail, 2010.. Effects of oral, vaginal and transdermal hormonal contraception on serum levels of coenzyme q(10), vitamin e and total antioxidant activity. Obstet Gynecol Int., 10.1155/2010/925635

Palmer, J.R., L. Rosenberg, D.W. Kaufman, M.E. Warshauer, P. Stolley and S. Shapiro, 1989. Oral contraceptive use and liver cancer. Am. J. Epidemiol., 130: 878-882.

Schaffir J.A., M.M. Isley and M. Woodward, 2010. Oral contraceptives Vs injectable progestin in their effect on sexual behavior. Am. J. Obstet Gynecol., 203: 545.e1-545.e5.

Sharma, R.S., M. Rajalakshmi, R.S. Sharma and D.A. Jeyaraj, 2001. Current status of fertility control methods in India. J Biosci., 26: 391-405.

Siddique, Y.H. and M. Afzal, 2004. Evaluation of genotoxic potential of synthetic progestin chlormadinone acetate. Toxicol. Lett., 153: 221-225.

Siddique, Y.H. and M. Afzal, 2005. Genotoxic potential of cyproterone acetate: A possible role of reactive oxygen species. Toxicol. *In vitro*, 19: 63-68.

Siddique, Y.H. and M. Afzal, 2008. A review on the genotoxic effects of some synthetic progestins. Int. J. Pharmacol., 4: 410-430.

Siddique, Y.H., G. Ara, T. Beg and M. Afzal, 2006. Genotoxic potential of medroxyprogesterone acetate in cultured human peripheral blood lymphocytes. Life Sci., 80: 212-218.

Siddique, Y.H., T. Beg and M. Afzal, 2005. Genotoxic potential of ethinylestradiol in cultured mammalian cells. Chem. Biol. Interact., 151: 133-141.

Siddique, Y.H., T. Beg and M. Afzal, 2007. Anticlastogenic effects of ascorbic acid against the genotoxic damage induced by norethynodrel. Adv. Environ. Biol., 1: 27-32.

Sinofsky, F.E. and S.A. Pasquale, 1998. The effect of fluconazole on circulating ethinyl estradiol levels in women taking oral contraceptives. Am. J. Obstet Gynecol., 178: 300-304.

Smith, J.L., G.A. Goldsmith and J.D. Lawrence, 1975. Effect of oral contraceptive steroids on vitamin and lipid levels in serum. Am. J. Clin. Nutr., 28: 371-376.

Speroff, L. and P.D. Darney, 1996. A Clinical Guide for Contraception. 2nd Ed. William and Wilkins, Baltimore, USA., Pages: 247.

Spona, J., N. Binder, K. Hoschen and W. Feichtinger, 2010. Suppression of ovarian function by a combined oral contraceptive containing 0.02 mg ethinyl estradiol and 2 mg chlormadinone acetate given in a 24/4-day intake regimen over three cycles. Fertil Steril., 94: 1195-1201.

Stoll, B.A., 1967. Effect of lyndiol an oral contraceptive on breast cancer. Brit. med. J., 1: 150-153.

Sulak, P.J., R.D. Scow, C. Preece, M.W. Riggs and T.J. Kuehl, 2000. Hormone withdrawal symptoms in oral contraceptive users. Obstet Gynecol., 95: 261-266.

Tzankova, V., V. Petrov and N. Danchev, 2010. Impact of oral contraceptives and smoking on arterial and deep venous thrombosis: A retrospective case-control study. Biotechnol. Biotechnol. Eq., 24: 2026-2030.

WHO, 1995. Venous thromboembolic disease and combined oral contraceptives: Results of international multicentre case-control study. World health organization collaborative study of cardiovascular disease and steroid hormone contraception. Lancet, 346: 1575-1582.

Walsh, B.W. and F.M. Sacks, 1993. Effects of low dose oral contraceptives on very low density and low density lipoprotein metabolism. J. Clin. Invest., 91: 2126-2132.

Webber, L.S, S.M. Hunter, J.G. Baugh, S.R. Srinivasan, M.C. Sklov and G.S. Berenson, 1982. The interaction of cigarette smoking, oral contraceptive use and cardiovascular risk factor variables in children: The Bogalusa Heart Study. Am. J. Public. Health., 72: 266-274.

Weiderpass, E., H.O. Adami, J.A. Baron, C. Magnusson, A. Lindgren and I. Persson, 1999. Use of oral contraceptives and endometrial cancer risk (Sweden). Cancer Causes Control., 10: 277-284.

White, T., J.K. Jain and F.Z. Stanczyk, 2005. Effect of oral versus transdermal steroidal contraceptives on androgenic markers. Am. J. Obstet Gynecol., 192: 2055-2059.

Wiegratz, I., K. Mittmann, H. Dietrich, T. Zimmermann and H. Kuhl, 2006. Fertility after discontinuation of treatment with an oral contraceptive containing 30 μg of ethinyl estradiol and 2 mg of dienogest. Fertil Steril., 85: 1812-1819.

Wynn, V., J.W.H. Doar and G.L. Mills, 1966. Some effects of oral contraceptives on serum-lipid and lipoprotein levels. Lancet, 288: 720-723.

Yeung, D.L., 1976. Relationship between cigarette Smoking, oral contraceptives and plasma vitamins A, E, C and Plasma triglycerides and cholesterol. Am. J. clin. Nutr., 29: 1216-1221.