THE EFFECT OF ORAL CONTRACEPTIVE AGENTS (OCA) ON NUTRITION

by 1050 710

PHYLLIS LATHROP

B. S., Hunter College of the City of New York, 1972

A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods and Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1974

Approved by:

Beth Fryer
Major Professor

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INTRODUCTION

Although recent reports have caused concern about the safety of oral contraceptive agents (OCA), statistics show that the mortality rate for "pill" users is 3 per 100,000. When this is compared with the mortality rate of 28 per 100,000 in pregnancy, and 25 per 100,000 in auto accidents, the risk seems small (1). There is increasing evidence that metabolic changes do occur, and present research is concerned with determining the severity and incidence of these changes (2). The metabolism of women receiving OCA is similar to that of pregnant women. Since the metabolic changes during pregnancy increase the requirements for some vitamins and minerals, the OCA user should have similar increased requirements. It is the purpose of this report to relate the findings of current research to the influence of oral contraceptive agents on nutrition.

HISTORY OF CONTRACEPTIVES

In 1937, Makepeace et al. (3) reported that ovulation in female rabbits could be inhibited as a result of treatment with the hormone, progesterone. In 1939, Sturgis and Albright (4) demonstrated that estrogen could inhibit ovulation in humans. For a number of years estrogen was used in the treatment of dysmenorrhea and menstrual irregularities. Evidence soon showed that estrogen couldn't be relied upon to regulate the cycle or to inhibit ovulation (5). The development of an effective oral contraceptive awaited the development of a progesterone-like synthetic hormone which was readily absorbed when given orally (6).

At a symposium on antifertility drugs in 1969, Drill (6) traced the history of oral contraceptives. Studies begun in 1952 by Colton and

Saunders at Searle Laboratories led to the development of the progestin of the first oral contraceptive. A second progestin was developed several years later by Djerrasi at Syntex Laboratories. These progestins and others developed since are used with estrogens and form the basis of the oral contraceptives that are currently in use.

A clinical trial of the first oral contraceptive, Enovid, in Puerto Rico was reported by Pincus in 1957 (7). Additional studies were carried out in Haiti and the United States. In 1957, Enovid was released for menstrual disorders; in 1960, it was approved as an oral contraceptive (8). The first oral contraceptive was a 10 mg. pill which contained progestin and a small amount of estrogen (8). Early pill users suffered side effects such as nausea, vomiting, large gains in weight and fluid retention, and thromboembolic disease. Since then new progestins have been introduced and the dosage has been reduced, thus eliminating many of the initial adverse side effects (8).

Because the cost is low, effectiveness is virtually 100%, and convenience is greater than other methods of birth control, the oral contraceptive has gained wide acceptance. At the present time it is estimated that more than 10 million women in the United States use this type of birth control (5).

FEMALE REPRODUCTIVE SYSTEM

Normal functions of the menstrual cycle. The menstrual cycle is a complex interplay between several hormones and between the endocrine and nervous systems (9). At the beginning of a new cycle (fig. 1), the uterine lining is thin and there are no ripe follicles in the ovaries. The first

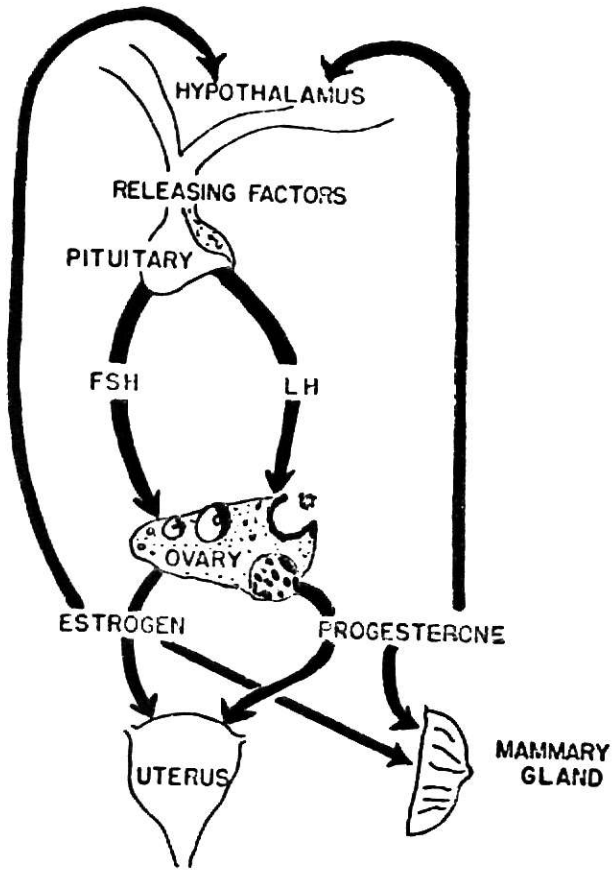

Fig. 1 Diagrammatic representation of interplay of sex hormones and gonadotropins in a normally cycling woman (8).

event in the new cycle is an increase in secretion of follicle-stimulating hormone (FSH) by the anterior pituitary. As a result of stimulation by the hypothalamus, FSH stimulates growth of follicles in the ovaries. The growing follicles begin secreting the first of the two female sex hormones, estrogen. The estrogen stimulates the lining of the uterus to thicken. This growth phase lasts, on the average, about nine to ten days.

As the follicles grow, they produce more estrogen. This increase in the level of estrogen in the blood exerts an inhibitory effect on the FSH-stimulating center in the hypothalamus. The result is a drop in secretion

of FSH by the anterior pituitary. The increased estrogen also stimulates the leuteinizing hormone (LH) center in the hypothalamus. The result is a decrease in FSH secretion and an increase in LH secretion. When the LH in the system has reached a peak level, ovulation occurs. Ovulation marks the end of the follicular phase of the menstrual cycle.

Following ovulation, LH induces changes in the follicular cells which convert them to a yellowish mass of cells called the corpus luteum. The corpus luteum continues to secrete estrogen but also begins to secrete a second female sex hormone, progesterone. Progesterone acts upon the uterine lining by causing it to thicken in preparation to receive the embryo. Progesterone also inhibits FSH secretion which would trigger the start of a new cycle.

If no fertilization occurs during the cycle, the high levels of progesterone inhibit the secretion of LH. When the level of LH in the system falls, the corpus luteum begins to atrophy and ceases to secrete progesterone. When this happens, the uterine lining can no longer be maintained and is sloughed off as the menstrual flow.

Functions during OCA use. When oral contraceptives are used, they act on the hypothalamus by causing production of FSH and LH to be held at a minimum (fig. 2). FSH and LH peaks do not occur, ovarian activity is minimal, and follicular maturation does not occur. The uterine lining is developed to a minimum and with withdrawal of the hormone pills, bleeding occurs (8).

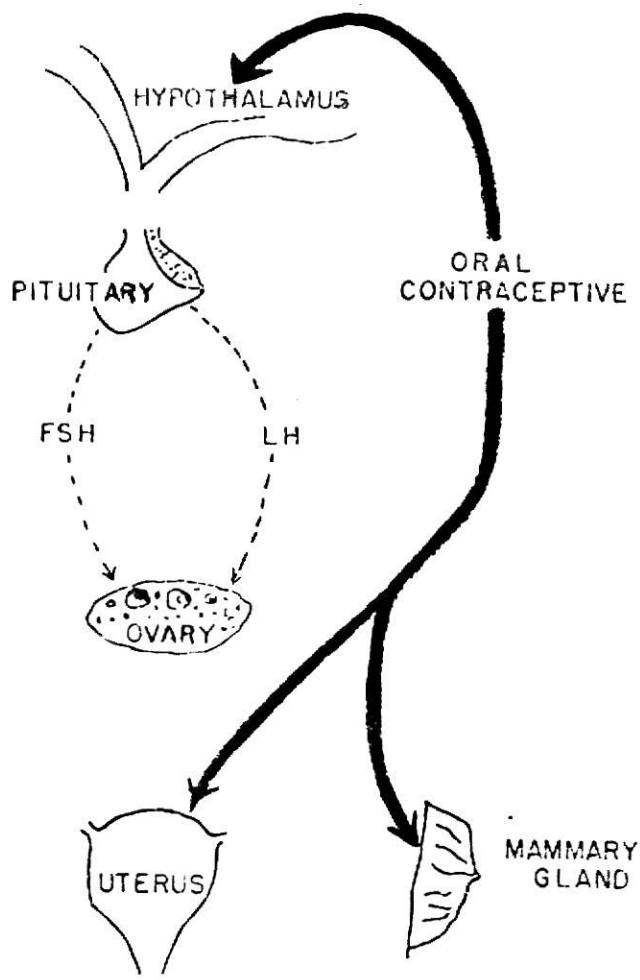

Fig. 2 Diagrammatic representation of effects of oral contraceptives (8).

COMPOSITION OF ORAL CONTRACEPTIVES

The basic composition of the pill is a combination of a synthetic progestin and an estrogen in different dosages (10). The synthetic estrogens used are menstranol and ethinyl estradiol. The progestins used are listed in table 1.

The majority of oral contraceptives fall into two categories; combined and sequential (10). Table 2 lists the currently available combined tablets. They are administered daily for 20 or 21 days. Bleeding occurs from three to

TABLE 1

Progestins employed in oral contraceptives (10)

C_{19}	Norsteroid derivatives
	Norethynodrel
	Norethindrone
	Ethynodiol diacetate
	Norgestrel
	Dimethisterone
	17-Hydroxyprogesterone derivatives
	Medroxyprogesterone acetate
	Chlormadinone

TABLE 2

Currently available combined oral contraceptives (10)

Trade name	Progestin and dose mg. per day	Estrogen and dose mg. per day
Enovid 5	Norethynodrel 5	Mestranol 0.075
Enovid E	Norethynodrel 2.5	Mestranol 0.10
Ovulen-21	Ethynodiol diacetate 1.0	Mestranol 0.10
Ovulen-28*		
Norinyl 2	Norethindrone 2.0	Mestranol 0.10
Norinyl-1 (Noriday*)	Norethindrone 1.0	Mestranol 0.05
Norinyl 1/80	Norethindrone 1.0	Mestranol 0.08
Ortho Novum 10	Norethindrone 10.0	Mestranol 0.06
Ortho Novum 2	Norethindrone 2.0	Mestranol 0.10
Ortho Novum 1	Norethindrone 1.0	Mestranol 0.05
Ortho Novum 1/80	Norethindrone 1.0	Mestranol 0.08
Provest	Medroxyprogesterone acetate 10.0	Ethinyl estradiol 0.05
Ovral	Norgestrel 0.5	Ethinyl estradiol 0.05
Norlestrin 2.5	Norethindrone 2.5	Ethinyl estradiol 0.05
Norlestrin 1 mg.	Norethindrone 1.0	Ethinyl estradiol 0.05
Norlestrin 28*		
Norlestrin Fe†		

*Days 22 to 28, seven inert tablets.

†Days 22 to 28, iron supplement tablets.

five days after the pills are stopped. A new cycle begins on the fifth day of bleeding when the pills are resumed for another 20 or 21 days.

In the sequential cycle, estrogen is administered for 14 or 16 days, followed by the combined progestin-estrogen composition or progestin alone for 5 or 6 days (10) (table 3). These preparations are less effective in suppressing ovulation but cause chemical changes in the cervical mucous and the endometrium that make implantation less favorable (5).

TABLE 3

Currently available sequential oral contraceptives (10)

Trade name	Progestin and dose mg. per day 21 to 25	Estrogen and dose mg. per day 5 to 25
Oracon	Dimethestrone 25	Ethinyl estradiol 0.10
C-Quens	Chlormadinone 2.0	Mestranol 0.08
Ortho Novum SQ	Norethindrone 2.0	Mestranol 0.08
Norquen	Norethindrone 2.0	Mestranol 0.08

EFFECTS OF OCA ON PROTEINS, LIPIDS, AND CARBOHYDRATES

Proteins. Craft and Wise (11) reported a significant fall in fasting plasma-α-amino-nitrogen in normal women between days 17 and 22 of the menstrual cycle as compared with days 2 and 7. The absence of significant aminoaciduria after ovulation suggested that this fall may be the result of greater utilization of amino acids for ovarian hormone production. There is an increased utilization of individual amino acids at this time. Soupart (12) reported a significant reduction of alanine, lysine, proline, serine, and threonine concentration during the luteal phase of the cycle. He also

found that women have greater tolerance to both oral and intravenous loads of glycine following ovulation. Evidence suggests that the progesterone secreted by the corpus luteum is responsible.

Craft (13) also found a significant fall in plasma-α-animo nitrogen in a group of women after the administration of OCA for 12 to 17 days. There was no increase in urinary nitrogen which suggested that there was an increased utilization. Since endogenous ovarian-hormone production was suppressed, the fall in plasma levels may be the result of anabolic effects of progestogens on tissue utilization. These results suggest that there is increased utilization of amino acids throughout most of the cycle while taking the pill; however, normal women have increased utilization only following ovulation. This fact may contribute to the tendency of OCA users to gain weight.

Mendenhall (14) measured concentrations of eight plasma proteins in women using a variety of oral contraceptives (table 4). The proteins measured were albumin, immunoglobulins G, A, and M, the metal-binding proteins transferrin and ceruloplasmin, α-2-macroglobulin, and α-1-antitrypsin. Results showed a significant decrease in albumin concentration and an increase in immunoglobulin M and α_1-antitrypsin. The changes in several other proteins were not significantly different from the control sera (table 4, column B).

In an attempt to determine whether estrogen was responsible for these changes, Mendenhall (14) studied an additional 30 women (table 4, column C). Fifteen of the women received ortho-novum 1 mg. (norethindrone 1 mg. and mestranol 0.05 mg.) and fifteen took ovulen 21 (ethynodiol diacetate 1 mg. and mestranol 0.1 mg.) for 6 months. When analyzing the entire group, albumin concentrations were found to be significantly decreased and

immunoglobulin M, increased (table 4). The elevations of transferrin and ceruloplasmin were not significantly elevated.

Mendenhall (14) showed that there were several points of similarity in the serum protein concentration of pregnant women at term and of women using OCA (table 4).

TABLE 4

Serum protein concentrations (14)

Column	A	B	C	D
	Controls or percent of pooled sera (25 nonpregnant women)	Variety of oral contraceptives (20 women)	Either 0.05 or 0.1 mg. of mestranol (30 women)	Term pregnancy
Albumin (mg. %)	4296 ± 451	3800 ± 463 $p < 0.001$	3905 ± 392 $p < 0.01$	3144 ± 709
Immunoglobulin G (mg. %)	1248 ± 408	1165 ± 291 $p > 0.4$	1366 ± 318 $p > 0.2$	1571 ± 598
Immunoglobulin A (mg. %)	241 ± 142	201 ± 100 $p > 0.2$	243 ± 142 $p > 0.95$	242 ± 146
Immunoglobulin M (mg. %)	89 ± 28	114 ± 46 $p < 0.05$	170 ± 90 $p < 0.001$	123 ± 53
Transferrin	100%	120 ± 34 $p > 0.5$	130 ± 35 $p > 0.3$	160 ± 49
Ceruloplasmin	100%	213 ± 61 $p > 0.05$	393 ± 157 $p > 0.05$	234 ± 67
α_2-Macroglobulin	100%	80 ± 17 $p > 0.2$	87 ± 25 $p > 0.5$	110 ± 34
α_1-Antitrypsin	100%	244 ± 46 $p < 0.01$	180 ± 38 $p > 0.2$	324 ± 90

Mean Values ± 1 S.D. Concentration of other proteins in per cent reference serum.

In another experiment to determine whether estrogen or progestogen was responsible for increases in macroglobulin, transferrin, and immunoglobulin G, Horne (15) studied 2 groups of 14 women. One group was given 50 mg. estrogen and the other, 1 mg. progestogen daily for 3 weeks. Protein levels were measured at weekly intervals before, during, and after therapy. A significant increase was found in α-$_2$-macroglobulin and transferrin in the group taking estrogen. Neither group showed significant changes in immunoglobulin G or albumin.

In a similar study Horne (15) measured the protein levels in 14 women who did not use OCA. Protein levels were measured at 3-4 day intervals over one cycle. Although no evidence of cyclical variation due to endogenous production of hormones was found, there was some indication that transferrin showed a cyclical variation.

Elstein (16) reported an increase in total protein content of the cervical mucus due to the progestational influence. The mucus acts as a barrier to the entry of spermatazoa in the upper genital tract. This suggests that proteins of the cervical mucus may contribute to a cross-linking mechanism between the glycoprotein fibrils in a bonding similar to that found in mucopolysaccharides. These cervical-mucus proteins provide an important function as a locally acting contraceptive.

Lipids. Since OCA produce changes similar to early pregnancy, they should produce increases in serum cholesterol and triglycerides (17). There is increasing evidence of a relationship between elevated levels of cholesterol and triglycerides and increased incidence of cardiovascular disease. However, premenopausal women are relatively immune to cardiac and cerebrovascular occlusive disease because of the presence of female hormones. The

concern arises over whether OCA when taken over a period of years will increase the incidence of cardiovascular disease in OCA users. Studies in 1965 and 1966 (17) indicated no change in serum cholesterol nor low density lipoproteins in women taking OCA. Studies since that time have revealed increased levels of either serum cholesterol or triglycerides. For example, for 12 weeks Johnson and Lee (17) studied 25 women who had never used OCA. Each woman was given a tablet containing 0.5 mg. norgestrel and 0.5 mg. ethinyl estradiol. They maintained a schedule of 3 weeks on the pill, and 1 week off. A 12-hour fasting blood specimen was taken before the study was begun, and fasting specimens were taken at two, four, and 12 weeks. Results showed a significant elevation of serum triglycerides in 18 of the 25 women at 12 weeks. Serum cholesterol was elevated in only three of the women.

Schenker (18) observed that progesterone had no significant effect on serum lipids. He also found no direct correlation between the length of OC therapy or the type of OCA used. Total serum lipids and triglycerides were increased but no change in cholesterol was found. Some studies (19-20) have concluded that estrogen diminishes the cholesterol/phospholipid ratio by increasing serum phospholipid concentration and/or lowering serum cholesterol levels. In hypercholesterolemic women, the administration of estrogen lowers serum cholesterol concentrations.

The following conclusions were drawn from a study of women taking three different combinations of OCA (21). The women were tested at three-month intervals for two years. A rise in serum cholesterol and triglycerides was seen in those taking combinations of estrogen and progesterone; no change was found in those taking progesterone alone. There was a greater rise in those on higher doses of combined pills; serum triglycerides rose more than

cholesterol. The rise began early in therapy and continued as long as OCA were used. When OCA were withdrawn for six months, there was a fall in serum lipids (21).

From these results, it appears that estrogen in OCA causes a rise in either serum cholesterol or serum triglycerides or both. The risk of cardiovascular disease may increase when OCA are used for prolonged periods of time (21).

Carbohydrates. As already mentioned, it is generally agreed that the most characteristic lipid alteration of OCA is an increase in serum triglycerides (17, 18, 21). Since insulin can increase the rate of synthesis of triglycerides in the liver, the primary alteration may be in carbohydrate metabolism with a secondary change in lipids. Evidence at this time shows that there is carbohydrate metabolic alteration in some women who take OCA. This abnormality shows elevations in glucose, insulin, nonesterified fatty acids, growth hormone, triglycerides, pyruvate, and cortisol. The mechanisms that produce these elevations are not known. Women who are most likely to develop changes in carbohydrate metabolism are those of older age, those who have infants of 9 pounds or more, and those who gain excessive weight while on the pill (22). Women who are from families with a history of diabetes mellitus are also more likely to have abnormal carbohydrate changes.

Estrogens tend to cause an excess secretion of insulin and growth hormone and to elevate glucose in normal women (22). The effect on glucose metabolism depends upon the type and dose of estrogen used. The progestins do not appear to have such a marked effect on carbohydrate metabolism.

Present studies on OCA and glucose metabolism are difficult to interpret. There are more abnormal glucose tolerance tests associated with the

combination agents than with the sequential types. However, there have been fewer and shorter duration studies made with the sequential types. The type of drug and the length of use seems to directly affect glucose intolerance.

Spellacy (23) studied 19 women who had used the pill for at least 5.4 years. Blood glucose, plasma insulin, and plasma growth hormone were measured after the women had maintained a high carbohydrate diet for three days. Results showed that glucose tests were normal in 75% of the women on sequential pills and 63% on the combination-type pill. Insulin and growth hormone levels were higher in those with high glucose levels, but growth hormone levels were suppressed as blood glucose levels rose.

The methods of alteration of carbohydrate metabolism are not known, but several hypotheses have been proposed (22). Plasma glucocorticoids are elevated in OCA users because of the action of estrogen, which raises the protein binding level. The rates of production of glucocorticoids and the metabolic clearing rates are lower in OCA users. Although this alteration has been found, it is doubtful that this alone is responsible for carbohydrate changes.

Since the liver is involved in glycogen storage and glucose release, researchers have studied liver function in relation to altered carbohydrate metabolism. Wynn and Doar (24) found that fasting blood pyruvate levels were elevated in 22% of the OCA users studied. This abnormality, in addition to raised triglyceride levels, could be a reflection of abnormal liver function.

Fasting plasma growth hormone levels are elevated by the action of estrogens (25). These high levels are probably the cause of impaired glucose tolerance since growth hormone has diabetogenic effects. Wynn and Doar (24) reported that the blood levels of nonesterified free fatty acids are

elevated after estrogen administration; this effect could also be a result of increased growth hormone activity (24).

Although glucose tolerance tests return to normal shortly after stopping OCA, insulin levels may remain elevated for some time (26). This suggests that the elevated insulin level may serve as a compensatory mechanism for the maintenance of glucose homeostasis. This fact raises the question of possible long-term effects of OCA. There is no worry of damaging the pancreatic beta cells of the juvenile diabetic since they generally produce little insulin (22). There is no contraindication of the use of OCA with insulin-dependent diabetic women. The question arises whether alteration of glandular function will produce permanent damage. Garcia (27) has stated that no overt diabetes has appeared in either the United States or Puerto Rico with 6 to 10 years of OCA use. This question must still remain a consideration until further research proves that there is no permanent damage.

EFFECTS OF OCA ON VITAMINS

Pyridoxine. Several of the enzymes involved in the metabolism of tryptophan to niacin require pyridoxal phosphate as a coenzyme (28). In pyridoxine deficiency increased amounts of tryptophan metabolites, xanthurenic acid, 3-hydroxykynurenine, and kynurenine are excreted in the urine after a tryptophan load test. The xanthurenic acid content of urine is an index for tryptophan metabolic intermediates (29).

In a study with female rats, 10 ug. doses of estrogen were shown to increase tryptophan oxygenase activity (30). These results suggest that estrogens have a direct effect in elevating the activity of tryptophan oxygenase. Similar findings by Rose (31) also indicate that estrogen is

primarily responsible for abnormal tryptophan metabolism, since a male subject receiving 0.1 mg. of estrogen daily for five weeks showed increased excretion of xanthurenic acid. Luhby (29) found that a daily dose of 25 mg. pyridoxine hydrochloride would normalize the urinary excretion of xantheurenic acid. He recommends 30 mg. a day for women who use OCA.

According to Green (32), an increased level of tryptophan oxygenase may result in a decreased availability of tryptophan for serotonin synthesis. Luhby (29) stated that depression may be related to a decreased production of serotonin. Depression is a common side effect of pregnancy and OCA use (2).

Baumblatt and Winston (33) studied 58 patients who had used OCA for an average of 14 months. Two to five days before menstruation, each had at least three of the following symptoms: emotional liability and irritability, depression, fatigue, mild paranoid ideation, and difficulty with concentration and sleep disturbance. Twenty-two had all five symptoms. Fifty had some symptoms before using OCA but these were either aggravated or new symptoms developed. During the study the subjects were told that they were to take the 50 mg. pyridoxine tablet at the first sign of symptoms. Of the 58 women, 18 stated that all of their symptoms disappeared, 26 stated that 2 symptoms were gone, and 14 showed no improvement. Those who reported improvement felt the results within an hour or the next day. In a follow-up study, the 14 subjects who showed no improvement with 50 mg. pyridoxine tablets were given 100 mg. They reported no change with the increased dose (33).

Riboflavin. Riboflavin is involved in the enzyme system that oxidizes pyridoxine phosphate to the metabolically active form, pyridoxal phosphate.

The need for riboflavin may increase when increased amounts of pyridoxine are needed (2).

Rose and McGinty (34) reported indirect evidence of the need for riboflavin increases with use of OCA. OCA administration results in increased plasma cortisol levels. Cortisol increases the excretion of abnormal tryptophan metabolites after a load dose much as estrogen does. Rose and McGinty (34) found that niacin and riboflavin partially normalized the metabolites in three of four women. Niacin alone was not effective; riboflavin alone was not tested. These results suggest that increased riboflavin would help normalize tryptophan metabolism.

Niacin. Rose (35) has postulated that estrogens induce an increase in the activity of the enzymes that convert tryptophan to niacin. Rose et al. (36) reported increased basal excretion of N-methyl-nicotinamide, a nicotinic acid metabolite, in women taking OCA. Increasing the yield of niacin from tryptophan would decrease the need for preformed dietary niacin.

Folic Acid. Folic acid deficiency, common in pregnancy, has been attributed to parasitisation by the fetus and hormonal factors (37). This deficiency is also seen in women on OCA. They have lower serum-folate levels and higher urinary formiminoglutamic acid (FIGLU) after histadine loading. Since women frequently become pregnant after stopping OCA, they may develop megaloblastic anemia or low folate levels may increase the incidence of abortion (38).

Strieff (40) found an abnormality of intestinal absorption of the dietary form of folate, polyglutamic folate, but no impairment of absorption of the pharmacologically available form, monoglutamic folate. It is believed that this malabsorption is a result of the inhibitory action of OCA

on the intestinal enzyme, folate conjugase. This enzyme must act before absorption can take place in the small intestine.

Strieff (39) studied 18 women, 9 who had taken OCA for at least a year and 9 who had never taken them. He found all the women had normal serum folate levels and that none was anemic. The absorption of monoglutamic folate did not seem to be affected, but the absorption of polyglutamic folate in women on OCA was 50% lower than the controls. The usual American diet contains more folate than is needed; folate deficiency in non-pregnant women is rare in the United States. But serious problems could arise in other populations where the intake of dietary folate is not so high.

Shojania suggests that women on OCA take 250 ug. folic acid daily (39). Strieff (40) also advises this supplement.

Vitamin B_{12}. Bianchine et al. (41) measured the serum binding capacity of B_{12} in 20 healthy term-pregnancy patients, 32 non-pregnant women who did not use OCA, and 62 women on OCA (table 5). Serum binding B_{12} capacity was increased during pregnancy and by OCA. No correlation was found between length of therapy and B_{12} binding capacity.

TABLE 5

Serum binding capacity of vitamin B_{12} (41)

Class of woman	Number	Binding capacity
Control	32	1606 ± 213 pg*/ml
2-3 days postpartum	20	2600 ± 572 pg/ml
OCA users	53	1877 ± 326 pg/ml

*Micromicrogram

Wertalik et al. (42) studied serum B_{12} levels in 20 women who had taken OCA for 2 to 60 months, 26 women in the last trimester of pregnancy, and 23 women who served as controls (fig. 3). The women taking OCA had a mean serum B_{12} level 40% lower than the control group. No statistical difference was found between the OCA group and those in the last trimester of pregnancy. The distribution of B_{12} values in women taking OCA showed that 50% had sub-normal values, 15% were clearly deficient (fig. 4).

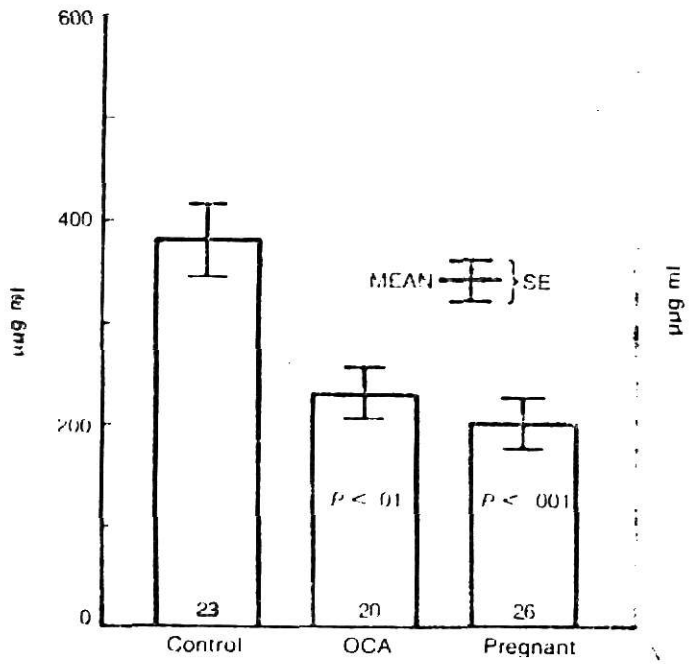

Fig. 3 Serum vitamin B_{12} levels for normal women, women taking oral contraceptive agents (OCA), and pregnant women. Number of subjects studied in each group is designated (42).

Unlike Bianchine (41) Wertalik et al. (42) found no increase in B_{12} binding capacity in OCA users. They suggested four possibilities for the decreased serum B_{12} values found in their study: (a) malabsorption, (b) increased renal excretion, (c) factors that interfere with the

radioisotope dilution assay for the vitamin and (d) increased tissue absorption.

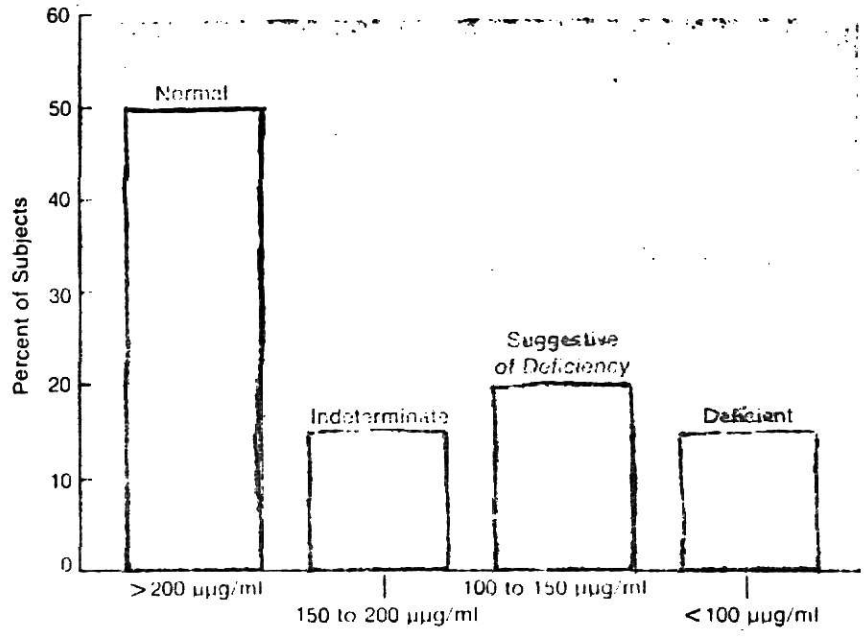

Fig. 4. Distribution of serum vitamin B_{12} values in 20 women taking OCA (42).

Vitamin A. Moore (43) has drawn attention to inverse relationships between vitamin A and copper in the later stages of pregnancy. The blood copper level increases during the last trimester of pregnancy but the blood vitamin A level decreases. However, Gal (44) found that plasma vitamin A levels of OCA subjects were significantly increased over those of non-pregnant controls. This increase suggests a higher vitamin A need for women taking OCA.

Vitamin C. Observations suggest that ascorbic acid metabolism is altered in OCA users (2). Briggs (45) studied blood vitamin C levels in 85 women who were either untreated, pregnant, or on OCA for 6 months to over 1

year. Ascorbic acid in leukocytes and platelets were significantly lower in women taking OCA than in those who were pregnant or untreated. Briggs suggested that OCA increased the breakdown of ascorbic acid--perhaps by the stimulant action of the liver release of ceruloplasm which has ascorbate oxidase activity. He also stated that women on OCA may be in a hypovitaminoic C condition and may require supplementation.

Similar results were found by McLeroy and Schendel (46) who studied 63 controls and 63 women who had taken OCA for 1 year. A 3-day dietary record was kept and blood samples were taken. The mean dietary vitamin C intake was 86 ± 45 mg. for the control group and 86 ± 48 mg. for the experimental group. Eight of the controls and 19 of the experimental group took vitamin C supplements. The vitamin C concentration of the leukocyte in the experimental group was significantly less than that of the control group; vitamin C supplementation had a significant effect in the control group but not in the experimental group. The data provides evidence that sex hormones influence ascorbic acid metabolism.

EFFECTS OF OCA ON MINERALS

Copper. The copper content of maternal blood increases during the later stages of gestation (47). Serum copper levels also increase with administration of OCA or estrogens (48). The green copper-carrying protein, ceruloplasmin, also increases so that the plasma of women taking OCA can have a green cast (49). The increases in ceruloplasmin and copper levels indicate an increased absorption of dietary copper. Increased ceruloplasmin suggests the need for vitamin A may be decreased by OCA (2).

Zinc. Halstead et al. (50) reported that pregnant women and women taking OCA had higher plasma zinc and copper levels than control women. The estrogen component of the OCA decreased plasma zinc levels in rats but increased zinc uptake by the liver, spleen, adrenals, and uterus. OCA may increase the zinc requirement.

Iron. Iron deficiency anemia is a common disorder in fertile women (51). The main reason is the loss of iron in menstrual bleeding. Since OCA produce a significant reduction in menstrual blood losses, a reduction in iron deficiency anemia could be expected. However, no significant increase in hemoglobin concentration has been found during OCA therapy (52). One reason for this may be that, as in pregnancy, plasma volume increases relatively more than the red cell mass. Serum iron concentration also increases during contraceptive therapy, but this increase does not seem to be related to the decreased menstrual loss (53). The question has been raised as to whether increased serum iron concentration is due to an increased absorption or to an increased mobilization of iron from tissue stores (54). Total iron binding capacity (TIBC) also increases during OCA therapy probably because of an increased protein synthesis (55).

It is evident that OCA produce significant increases in serum iron, TIBC, and decreases in menstrual losses (51). Therefore, it is of interest to study the absorption of iron before and during OCA therapy. The absorption of iron before and during contraceptive therapy was investigated in 6 women who had never used OCA. Phlebotomies of 400 ml. were taken 4 times from each subject. Two absorption studies were made before oral contraceptives were administered. The first one was made during basal conditions and the second one, 12 days later, after the phlebotomy. This blood was then

reinfused to re-establish the basal conditions (table 6). The basal absorption during contraceptive therapy was unchanged when compared to the basal absorption before treatment. Results (table 6) indicate that there was no increased plasma iron concentration during OCA therapy.

TABLE 6

Haemoglobin concentration (g/100 ml) and haematocrit (%) (51)

	Before oral contraceptive				During oral contraceptive			
	Basal		After phlebotomy		Basal		After phlebotomy	
Subject	Hb	Hcr	Hb	Hcr	Hb	Hcr	Hb	Hcr
1	12.5	39	11.5	36	11.1	35.5	11.4	36
2	11.2	35	10.3	33	11.0	36	10.3	34
3	11.7	37	12.0	37	12.0	38	10.9	36
4	12.5	38	12.2	35.5	13.0	39	11.8	36
5	13.2	40	12.8	38	13.2	41	12.6	39
6	14.8	42.5	13.0	37	14.2	42	12.9	38
Mean	12.7	38.6	12.0	36.1	12.4	38.6	11.7	36.5

Plasma iron concentration and the TIBC are shown in table 7. The mean basal plasma iron concentration and TIBC increased significantly during contraceptive therapy. This increase was apparently due to hormonal influence. Similar results were found by Thein et al. (53).

Menstrual blood losses from two menstrual periods were measured before beginning OCA therapy (table 8). Mean values of menstrual blood loss decreased significantly after 4 menstrual periods on OCA.

TABLE 7

Plasma iron (ug/100 ml) and TIBC (ug/100 ml) (51)

	Before oral contraceptive				During oral contraceptive			
	Basal		After phlebotomy		Basal		After phlebotomy	
Subject	Plasma iron	TIBC	Plasma iron	TIBC	Plasma iron	TIBC	Plasma iron	TIBC
1	104	371	83	373	88	414	36	481
2	44	392	18	387	78	431	20	453
3	83	283	38	358	161	401	72	483
4	76	297	67	353	174	391	101	421
5	185	226	74	254	228	322	-	-
6	206	281	51	264	181	337	133	344
Mean	116	308	55	332	152	383	72	436

TABLE 8

Amount of menstrual blood losses (ml) (51)

	Before oral contraceptive		During oral contraceptive			
Subject	I	II	I	II	III	IV
1	80.5	53.0	58.6	21.0	16.1	14.7
2	82.8	49.6	40.6	25.1	19.8	21.5
3	77.6	70.3	9.6	18.5	6.7	10.6
4	17.9	24.1	7.2	6.1	6.0	3.2
5	24.3	12.8	15.2	10.0	6.7	8.0
6	13.0	8.3	1.9	1.5	0.2	3.0
Mean	49.4	36.4	22.2	13.7	9.3	10.2

Individual and mean values of iron absorption of a test dose of 0.56 mg. Fe++ are given in table 9. In all subjects the phlebotomy induced increased absorption. During contraceptive therapy absorption was almost the same both in basal and after phlebotomy. These results indicate that there was no increased absorption of iron during OCA use. Norrby et al. (51) concluded that the elevation of plasma iron concentration was due to an increased mobilization of iron from the body stores.

TABLE 9

Absorption of iron (% of administered test dose: 0.56 mg. Fe++) (51)

	Before oral contraceptive		During oral contraceptive	
Subject	Basal	After phlebotomy	Basal	After phlebotomy
1	65.4	92.6	69.2	82.6
2	80.1	91.5	89.3	98.0
3	46.7	91.1	61.9	88.2
4	48.4	95.8	7.8	68.9
5	39.2	70.4	27.9	65.9
6	36.9	52.0	54.6	77.4
Mean	52.8	82.2	51.8	80.2

Calcium and Magnesium. It has been reported that during OCA therapy, serum levels of calcium and magnesium are decreased. Thin (58) studied calcium and magnesium levels in women with normal menstrual cycles and women who used OCA. Alterations in the concentrations of naturally occurring hormones of the menstrual cycle did not appear to affect the levels of calcium or magnesium. Treatment with OCA for periods of 1 to 4 years did

not appear to have any effect on plasma calcium or magnesium. Thin stated that previous reports of lowered levels were based on OCA which had higher doses of estrogen than those used at the present time.

FURTHER ADVANCES IN HORMONE CONTRACEPTION

Because OCA are not ideally suited for certain segments of the world population, researchers have continued to look for a method of birth control that does not produce the side effects of estrogen and progesterone combinations.

One of these agents is Depo-Provera, medroxyprogesterone acetate, which is injected intramuscularly every 90 days (59). Medroxyprogesterone acetate is a synthetic progesterone which has been used since 1960 for the treatment of endometriosis and habitual abortion (59). In 1963 clinical studies were begun on 3,857 women to determine the optimum dosage schedule, efficacy, safety, patient acceptance, and type and incidence of side effects. Each woman received a single deep intramuscular injection of 150 mg. Subsequent injections were given at 90-day intervals (59). Results demonstrated that medroxyprogesterone acetate used at this dosage was well accepted and tolerated by women even though it produced amenorrhea or irregular menses in a high percentage of them. No major adverse reactions were found. Minor side effects were comparable in type and frequency to those reported for OCA. An advantage over OCA appears to be the freedom from the necessity to remember to take medication daily. Following discontinuation of therapy, fertility returned to normal (59).

A similar sustained-action contraceptive is the once-a-month pill. This pill is a combination of two mg. quinestrol and 2.5 mg. quingestanol acetate

referred to as QQ which is given every four weeks (60). Quinestrol is an estrogen which has prolonged activity due to its storage and subsequent release from body fat. Quingestanol acetate is a progestogen similar to norethindrone acetate but has twice its potency. A three year clinical trial took place in Lima, Peru using 1,084 young women. The overall rate of pregnancy during the study was 3.8 per 100 women (60). Cumulative protection rate against pregnancy was 95 per cent up to cycle 18 and 93 per cent after 24 cycles. The main side effects were amenorrhea, spotting, breakthrough bleeding, nausea, and vomiting. Patient acceptance was excellent; only 21 per cent discontinued treatment for drug-related reasons.

Still another type of OCA is the "mini" pill which contains only progesterone and is ingested each day (61). Although the failure rate is not so effective as the regular OCA, for women who have side effects from other OCA's and intra uterine devices, the mini pill is a useful alternative. The mode of action was at first thought to be that the cervical mucus changed so that it was in a "non-ovulatory" state and the *spermatozoa* were prevented from migrating through the cervix. More recent studies by many investigators have showed that some corpus lutea are normal. Fertility control appears to be complex and varies with the progesterone, the dosage, and the individual patient. In a clinical test, Nelson (61) studied the effect of the "mini" pill on 342 women. He found the general acceptance of the pill to be good; only 21 per cent quit the program because of dissatisfaction with the medication. Side effects other than menstrual irregularity were rare. With the estrogen component lacking, usual OCA side effects such as nausea, bloating, weight gain, fluid retention, pill-related miagraine and hypertension, thrombophlebitis, and alteration of carbohydrate metabolism were not seen.

These newer methods appear to have advantages for at least some women; however, the conception rate is higher than with the estrogen-progestogen combinations.

SUMMARY

There is increasing evidence that metabolic changes occur in oral contraceptive agent (OCA) users. Most of these changes are attributed to the estrogen component of the OCA. This report relates the findings of current research to the influence of OCA on metabolism and nutrient requirements.

There is evidence that metabolism of proteins, lipids, and carbohydrates are altered by OCA. Administration of various OCA resulted in a fall in plasma-α-amino nitrogen but no increase in urinary nitrogen suggesting that there is increased utilization of amino acids. Increases in serum triglycerides have been observed but increases in serum cholesterol have been found in only a few cases. Estrogens tend to cause an excess secretion of insulin, growth hormone, and glucose which is evidence of altered carbohydrate metabolism.

OCA affects the metabolism of various vitamins. OCA induce an increase in the activity of the enzymes that convert tryptophan to niacin. Several of these enzymes require pyridoxal phosphate as a coenzyme. The need for riboflavin also increases since it is involved in the conversion of pyridoxine phosphate to the metabolically active form, pyridoxal phosphate. Folic acid deficiency is seen in women taking OCA. This deficiency may be caused by an abnormality of internal absorption of the dietary form of folate, polyglutamic folate. Serum B_{12} binding capacity has been found to increase in

pregnancy and during OCA therapy; decreased serum B_{12} values have also been found in pregnant women and women on OCA. Increased plasma vitamin A levels of OCA subjects suggest that vitamin A needs may be increased during OCA use. Vitamin C in leukocytes and platelets were lower in women on OCA.

OCA also affects the metabolism of various minerals. Blood serum levels of copper and zinc are increased during OCA therapy. Serum iron and total iron binding capacity are increased with OCA therapy. This may be due to decreased menstrual losses and increased mobilization from body stores. It has been reported that serum levels of calcium and magnesium are decreased during OCA use; however, recent studies show no alteration.

Although a majority of women are able to take OCA without serious side effects, alterations of metabolism appear to be caused by the estrogen component. New low-dose, once-a-month pills, or injections of progestin provide somewhat less reliable contraception without causing metabolic alteration.

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THE EFFECT OF ORAL CONTRACEPTIVE AGENTS (OCA) ON NUTRITION

by

PHYLLIS LATHROP

B. S., Hunter College of the City of New York, 1972

AN ABSTRACT OF A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods and Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1974

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