NUTRITION DURING ORAL CONTRACEPTIVE TREATMENT

by

ANNIE CHI-YEE SIU

B.S., MISSISSIPPI UNIVERSITY FOR WOMEN, 1975.

A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods & Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1977

Approved by:

Jan J Carl

Major Professor

TABLE OF CONTENTS

THIS BOOK CONTAINS NUMEROUS PAGES WITH DIAGRAMS THAT ARE CROOKED COMPARED TO THE REST OF THE INFORMATION ON THE PAGE.

THIS IS AS RECEIVED FROM CUSTOMER.

INTRODUCTION

Oral contraceptives have been available since the early 1960s. In 1974, it was estimated that about 10 million women in the United States were taking these medications for fertility control (1). Because of their low cost, virtually 100% efficacy and greater convenience than other methods of birth control, oral contraceptives have gained wide acceptance.

The metabolism of women receiving oral contraceptives is similar in many respects to that of pregnant women. Since the metabolic changes during pregnancy are responsible to some extent for the increased vitamin and mineral requirements of pregnant women (2), the oral contraceptive user should have vitamin and mineral requirements more similar to those of the pregnant woman than to those of the non-pregnant woman not taking steroids. The purpose of this report is to relate the findings of current research on the effects of oral contraceptives and their ingredients, estrogen and progestin, upon nutrition.

TYPES OF ORAL CONTRACEPTIVES

Oral contraceptives fall into three major regimens: combined, sequential, and continuous progestin. In the combined regimen, a progestin and an estrogen combined in a tablet are administered daily for 20 or 21 days. In the sequential regimen, an estrogen is administered for 14 to 16 days followed by the daily administration of the combined estrogen and progestin tablet for 5 or 6 days (4). Tables 1 and 2 list the composition and dosages of the commonly available contraceptive medication (3). Both types of treatment inhibit ovulation and at the same time supply sufficient exogenous sex hormones, estrogen and progestin, so that the endometrium is developed and maintained.

Table 1: Combined Oral Contraceptives (3)

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.

Table 2: Sequential Oral Contraceptives (3)

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

Estrogens used in oral contraceptives consist of either ethinyl estradiol or its methyl ester, Mestranol. The progestins employed are structurally related to 19-nortestosterone, 17-hydroxyprogesterone derivatives,

medroxyprogesterone acetate and chlormadinone. The continuous daily administration of a progestin, Chlormadinone, in a dose of 0.5 mg. per day, or Norgestral, in a dose of 0.05 mg. per day has been found effective, but their widespread acceptance may be delayed by the higher incidence of bleeding irregularities encountered with their use (5).

EFFECT OF ORAL CONTRACEPTIVES ON FEMALE REPRODUCTIVE SYSTEM

At the beginning of a new menstrual cycle for an untreated non-pregnant woman, the uterine lining is thin and there are no ripe follicles in the ovaries. Anterior pituary hormone acts on the hypothalamus which gradually increases the secretion of follicle-stimulating hormone (FSH), which in turn, causes growth of follicles in the ovaries. The growing follicles begin secreting estrogen which stimulates the lining of the uterus to thicken and also stimulates the leuteinizing hormone (LH) center in the hypothalamus. This leads to a decrease in FSH secretion and an increase in LH secretion. When the LH has reached a peak level, ovulation occurs (6).

Following ovulation, the follicular cells are converted to corpus luteum which begins to secrete progesterone. If no fertilization occurs during the cycle, the high levels of progesterone inhibit the secretion of LH. When this happens, the uterine lining can no longer be maintained and is sloughed off as the menstrual flow.

It is generally agreed that when oral contraceptives are used, they cause an inhibition of ovulation and that this effect occurs by means of control of pituitary gonadotropin secretion. Cargille and Ross (7) have shown that the combined preparations inhibit the early FSH elevations and

abolish the midcyclic LH and FSH peaks. The sequential preparations interfere with the cyclic secretions of FSH and LH. Changes in plasma levels of FSH and LH do not necessarily mean that the pituitary gland is the site of action. In fact, the actual site of action may be the hypothalamus.

Oral contraceptives produce definite changes in the endometrial glands and stroma that could prevent implantation of the blastocyte (3). Another area of the reproductive tract affected by oral contraceptives is cervical mucus. The most important change induced by the progestin is in cervical mucus which inhibits sperm migration (8).

EFFECTS OF ORAL CONTRACEPTIVES ON PROTEINS, CARBOHYDRATES AND LIPIDS

Proteins. During the progestational phase, urinary nitrogen excretion is greater in ovulatory than in non-ovulatory cycles; and there is no increase in amino acid nitrogen. It was suggested that this increase in urinary nitrogen is chiefly urea (9). Craft and Wise, noting a decrease in plasma amino-acids in those women taking oral contraceptives, concluded that the catabolic effect of progesterone is the result of increased amino-acid utilization by the liver and also by peripheral tissues (9). This may be associated with the tendency to gain weight on an oral contraceptive regimen. This weight gain represents an increase in lean tissue and not merely fluid retention.

To determine whether estrogen or progestogen was responsible for the increases in macroglobulin, transferrin and immunoglobulin G, Horne (10) found that serum levels of alpha-2-macroglobulin and transferrin were raised in the group taking estrogen, but there were no significant changes

in albumin and immunoglobulin G.

Recently, Spellacy found a decrease in plasma albumin and increases in the alpha and beta globulins and fibrinogen with oral contraceptive use (11). The fall in albumin is attributed to a decrease in synthesis, as no considerable change in catabolism had been noted. Plasma volume did not change appreciably in response to the fall in albumin (11). The cortisol-binding globulin (CBG), thyroid-binding globulin (TBG) and carrier proteins for copper and iron, ceruloplasmin and transferrin, increased with oral contraceptive use.

The rise in blood pressure seen in some women "on the pill" may be attributed to the increase in an alpha-2-globulin, angiotensionogen I, which is converted by rennin to angiotensin II, a potent vasoconstrictor (11).

With the antiplasmic activity of alpha-2-macroglobulin, these findings may be relevant to the tendency to thrombosis associated with oral contraceptives (10, 13). In contrast, Pollar and Thomson (12) found a decrease in clotting tendency in women who changed from an estrogen-containing oral contraceptive to one containing only a 17-acetoxy-progestogen.

Briggs and Briggs (13) noted that the effects of Mestranol on serum protein were significantly less than those of oral Ethinyl estradiol. With the addition of 1.0 mg. Norethindrone to either estrogen, there was no effect in serum protein concentration when given alone, but a daily dose of 10.0 mg., a ten-fold increase, of Norethindrone induced changes unlike those produced by estrogen. They observed increase in ceruloplasmin and decreases in albumin, haptoglobin and orosomucoid which were largely dose-dependent.

After administration of an oral dose of L-tryptophan, women who are taking combined estrogen-progestogen preparation for contraceptive purposes excrete grossly increased quantities of xanthurenic acid, other tryptophan metabolites and N-methyl-nicotinamide in the urine (14). Rose (14) suggested that high tryptophan-oxygenase activity could cause low plasma-tryptophan with reference to depression and low brain 5-hydroxytryptamin.

Elstein (15) reported an increase in the protein of cervical mucus and suggested that such protein may contribute to the cross-linking mechanism between the glycoprotein fibrils of cervical mucus in a similar way to that which occurs in the bonding between mucopolysaccharides. Thus, cervical mucus protein provides a useful mean of evaluating low-dose progestogens which are being developed as locally active oral contraceptives.

Kalesh *et al.* (16) placed two groups of women on a low ascorbic acid diet, and found that women taking oral contraceptives exhibited significantly lower platelet amino acid levels than the control group. This decline in platelet amino acid could be due to increased excretion of amino acids or to the increase in concentration of ascorbate oxidase ceruloplasmin.

Carbohydrates. Glucose metabolism may be altered in women by continual use of contraceptive steroids. The changes in glucose tolerance are related to the combination of steroids employed, the dosage, the duration of therapy and the ability of the individual's pancreas to increase insulin production (17). However, the changes in glucose tolerance are usually small and are related to age.

Spellacy *et al.* (18) showed that neither Mestranol nor Ethinyl estradiol produced a change in oral glucose tolerance in normal women after 6 months of treatment, even though an increase in fasting serum growth hormone concentration was observed. Goldman *et al.* (19) observed no significant

changes in carbohydrate tolerance in normal women treated with Medroxy-progesterone acetate, a progesterone derivative. However, Spellacy *et al.* (20) found a slight deterioration in glucose tolerance with concurrent increase in plasma insulin concentration in normal women six months after receiving a single large injection of Medroxyprogesterone acetate. Nevertheless, neither the synthetic estrogen nor Chlormadinone acetate treatment produced any significant changes in the serum insulin responses to a glucose challenge in women (18).

No significant alteration in glucose utilization was observed by Larsson-Cohn *et al.* (21) in women treated with a small dosage of Norethindrone daily for one year. However, Spellacy *et al.* (22) observed deterioration of oral glucose tolerance in 13% of normal women after six months of treatment with Ethynodiol diacetate (a nortestosterone derivative).

Mestranol appears to potentiate the hyperglycemic effect of nortestosterone derivatives in normal women. Those using control pills that contained a nortesterone derivative for one year developed a greater incidence of deterioration of carbohydrate tolerance than women using agents that contained a synthetic derivative of progesterone (23). On the other hand, Starup (24) found a significant change in glucose utilization in women treated with sequential administration of contraceptive steroids.

Phillips and Duffy (28) did a study of 1,772 women using a variety of birth control pills. They noted that the alteration in carbohydrate tolerance was age-related, but it appeared to be unrelated to the type or dosage of the estrogen employed (Figure 1).

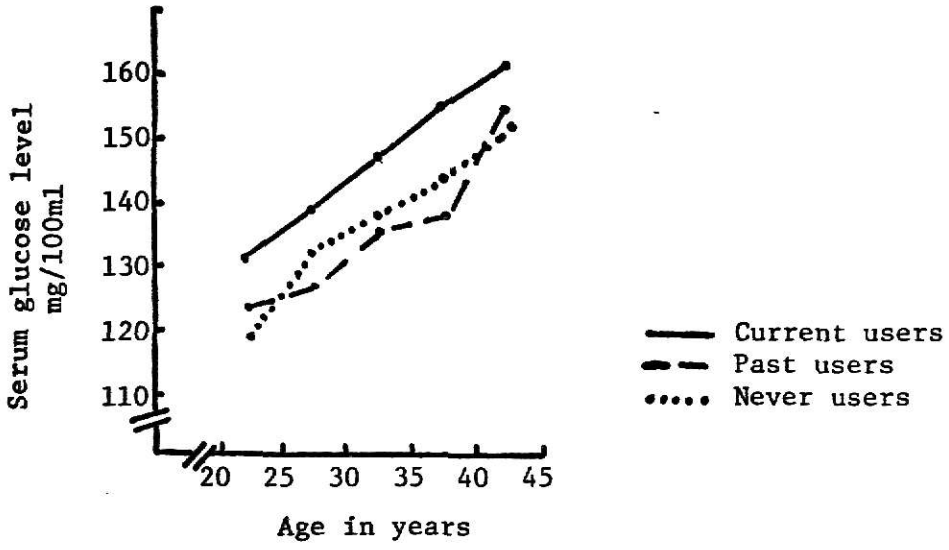

Figure 1. Mean serum glucose concentrations after oral glucose in current, past, and nonusers of contraceptive steroids adjusted for age (28).

Estrogen tends to cause an excess secretion of insulin and growth hormone (23, 26). Insulin and growth hormone levels were higher in those with high glucose levels, but growth hormone levels were suppressed as blood glucose levels rose (26).

The methods of alteration of carbohydrate metabolism are not known, but several hypotheses have been proposed (25). Plasma glucocorticoids are elevated in oral contraceptive 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 oral contraceptive users. Although this alteration has been found, it is doubtful that it alone is responsible for carbohydrate changes.

It is well recognized that the liver is involved in carbohydrate metabolism with glycogen storage and glucose release. Wynn and Doar (27)

reported that the fasting blood pyruvate levels are elevated in women taking oral contraceptives. This change might be explained by abnormal liver function.

Several studies have demonstrated that on discontinuing the use of oral contraceptives, the glucose tolerance tests in diabetic women will return to normal, yet insulin levels may remain elevated for some time (23, 25, 28). 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 oral contraceptives.

Lipids. Early work by Furman *et al.* (29) demonstrated that estrogen raised serum triglyceride concentration in postmenopausal women. Later, Gustafson and Svanborg (30) produced an increase in fasting plasma triglyceride and very low density lipoprotein (VLDL) concentrations with estrogen administration. Glueck *et al.* (31) demonstrated that Norethindrone acetate lowered triglyceride concentrations. However, Larsson-Cohn *et al.* (21) did not find significant alterations in fasting serum triglyceride concentrations in normal subjects treated with either Norethindrone acetate 5 mg/day or Norethindrone 0.4 mg/day, respectively. No changes in triglyceride metabolism have been observed when progesterone derivatives have been used as the sole contraceptive agent (32).

Although birth control pills containing combinations of synthetic estrogens with a synthetic progestin generally increased fasting serum triglyceride concentration, birth control pill combinations containing nortestosterone derivatives generally produced a smaller change in circulating triglycerides than those containing progesterone derivatives (21). Data presented by Stokes and Wynn (33) demonstrated that the hypertriglyceridemic effects of Mestranol and Ethinyl estradiol are dose-related (Figure 2).

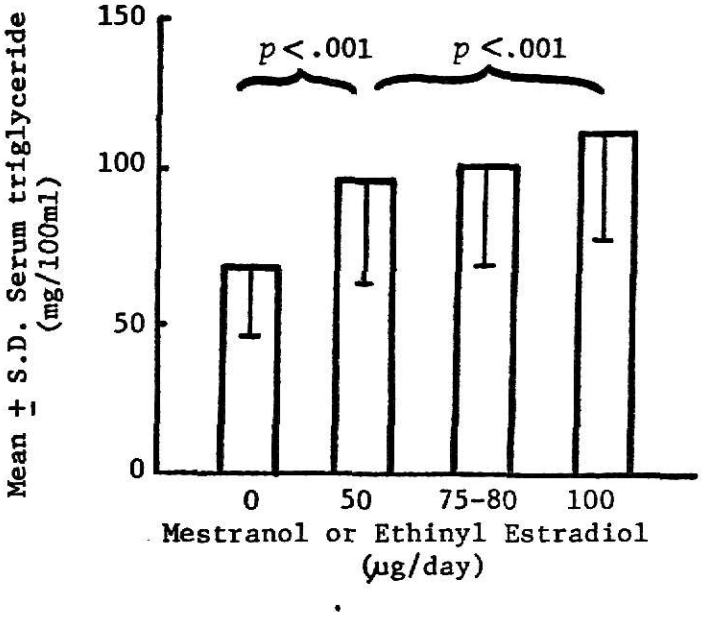

Figure 2. Relation of estrogen dose to fasting serum triglyceride concentrations in women using birth control pills containing Mestranol or Ethinyl estradiol plus a derivative of nortestosterone or progesterone (33).

They also showed that increasing doses of Norethindrone acetate may increasingly counteract the hypertriglyceridemic effect of a single dose of synthetic estrogen (Figure 3).

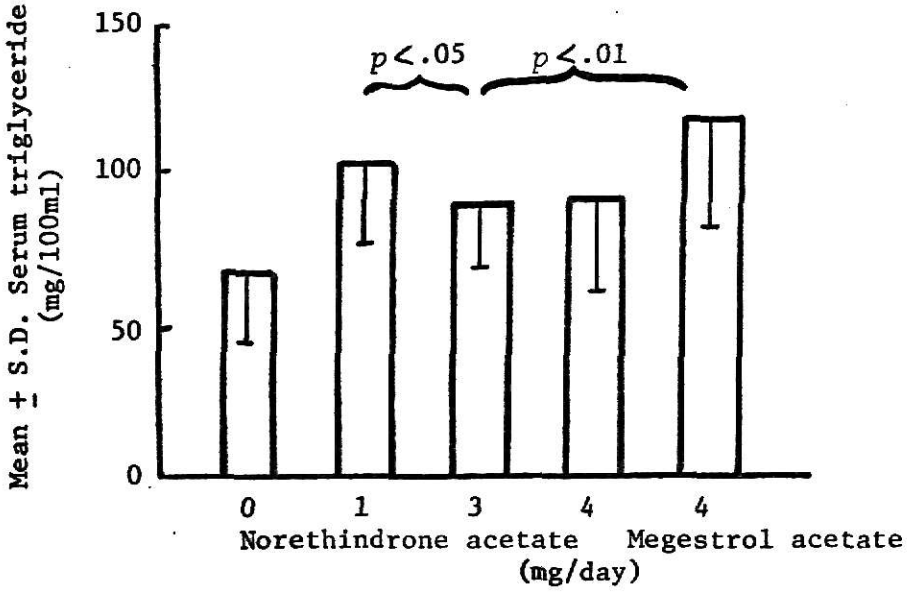

Figure 3. Norethindrone and Megestrol acetate modification of the hypertriglyceridemic effect of ethinyl estradiol (33).

The mechanism by which contraceptive steroids elevate serum triglyceride concentration is still not entirely clear. Earlier work by Hazzard *et al.* (34) demonstrated that the plasma clearing rate of triglycerides may be impaired in women using contraceptive steroids. In 1971, Kekki and Nikkila (35) demonstrated that triglyceride production and removal rates are accelerated in women using combined oral contraceptives. This suggests that the increases observed in serum triglyceride concentrations were due to a rate of triglyceride synthesis which exceeded the removal rate.

As mentioned earlier, the increase in serum triglyceride concentrations observed in women using contraceptive steroids appears predominately in the very low density lipoprotein (VLDL) fraction, the lipoprotein fraction generally presumed to be synthesized in the liver. Thus, increased hepatic production of triglycerides appears to be the critical factor determining the increase in serum triglyceride concentrations produced during contraceptive steroid use (30).

With regard to cholesterol metabolism, Spellacy *et al.* (18) suggested that contraceptive steroids alter serum cholesterol only a small amount. As shown by Stokes and Wynn (33), the modest increase in serum cholesterol concentration observed in users of estrogen-progestin combinations did not appear to be realted to the synthetic estrogen dose (Figure 4). However, increasing doses of Norethindrone with daily Ethinyl estradiol are associated with increasing fasting serum cholesterol concentrations at a constant dose of estrogen (Figure 5).

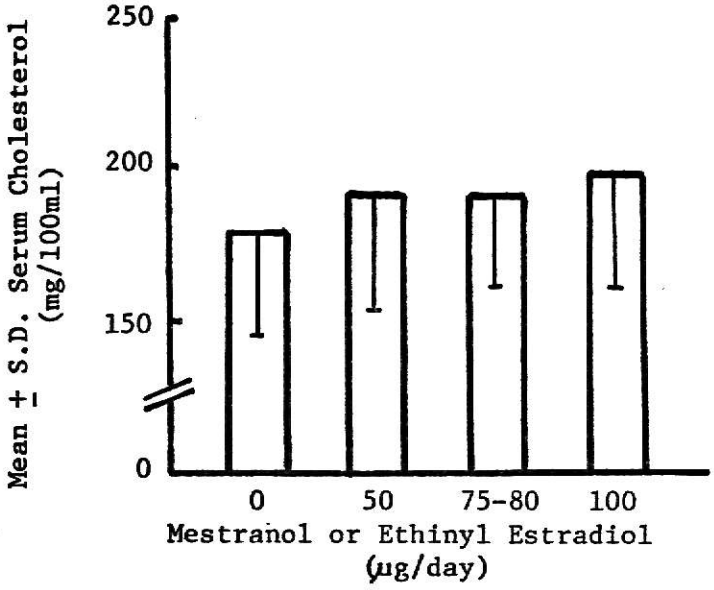

Figure 4. Relations of estrogen dose to fasting serum cholesterol concentrations in women using birth control pills containing mestranol or ethinyl estradiol plus a derivative of nortestosterone or progesterone (33).

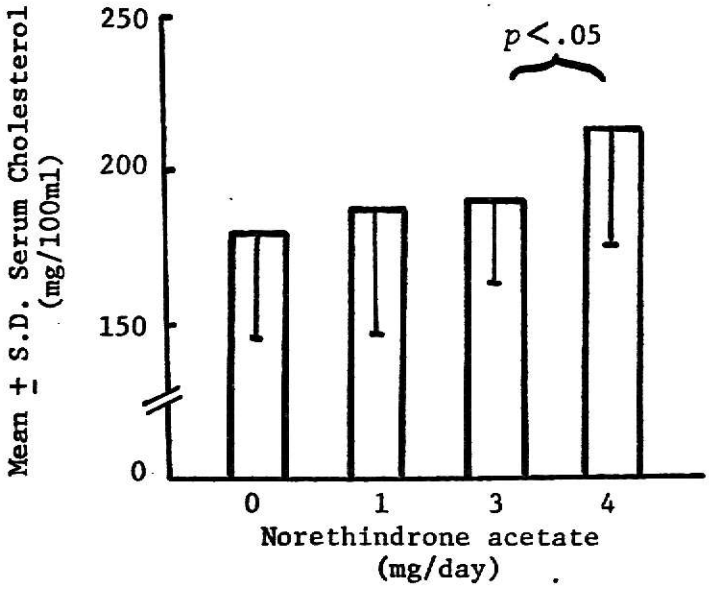

Figure 5. Relation of norethindrone acetate dose to fasting serum cholesterol concentrations when administered to women with ethinyl estradiol 50 μg/day (33).

The mechanisms by which contraceptive steroids alter cholesterol metabolism are obscure, although they appear related to age and ovarian function. Aitken and co-workers (36) showed that in young women, oophorectomy led to an increase in circulating cholesterol, but not in women over 46. In postmenopausal women, both ethinyl estradiol and conjugated estrogen increase the cholesterol content of HDL but lower the cholesterol content of LDL. Testosterone derivatives increase LDL cholesterol content and lower HDL cholesterol content (29). Thus, the mechanisms by which contraceptive steroids alter the normal aging pattern of cholesterol metabolism in women and the pathologic significance of these changes remain to be determined.

EFFECTS OF ORAL CONTRACEPTIVES ON VITAMIN FUNCTIONS

Folic acid. Shojania *et al.* (37) reported in 1968 that many women taking oral contraceptives have low levels of serum folate, thereby focusing attention on a possible interaction between these drugs and folate metabolism. This was followed by a number of reports of megaloblastic anemia in women using these agents. Streiff in 1970 described megaloblastic anemia in seven women who had been taking oral contraceptives for more than one year (38). Serum folate levels in these women were low, and B_{12} levels were normal. Subsequent articles described no significant differences in plasma folate levels between users of oral contraceptives and nonusers (39, 40). However, others have objected to these conclusions (41). Shojania *et al.* (39, 41) found, after a histidine load in oral contraceptive users, lower plasma and erythrocyte folate concentrations plus a greater 12-hour urinary formininoglutamic acid (FIGLU) excretion. These indicators often improved

after discontinuation of medication (41).

The possible effects of oral contraceptives on folate metabolism, as indicated by other studies of serum folate concentrations, may therefore be mild but could assume considerable importance in subjects with gastrointestinal disease and decreased absorption of folate, women with marginal dietary folate intake, and those who subsequently become pregnant and then have an increased requirement for folic acid (37).

Impairment of absorption of conjugated folate by oral contraceptives initially appeared to be a likely possibility. Streiff (38) measured serum folate levels after a administration of free folic acid in nine normal women and in nine other women who had been taking oral contraceptives for at least one year. He found similar rises in serum folate in both groups. In contrast, when the same women were given yeast folate polyglutamate orally, the rise in serum folate was less in the women taking oral contraceptives.

The findings of Stephens *et al.* (39) were similar, but they also reported that if tissues are saturated with folate before testing, folate polyglutamate absorption, as measured by rises in serum folate monoglutamate, was of the same degree in women using oral contraceptives and in those who were nonusers. The hypothesis that contraceptive steroids might interfere with folate deconjugation in the small intestine was examined by Stephens *et al.* (39). Estradiol, estrone, and progesterone were found not to inhibit folate conjugase in these systems or to inhibit transport of folate conjugase across lysosomal membranes.

Little is known about other aspects of folate metabolism, such as the factors that determine plasma clearance in either normal subjects or users of oral contraceptive steroids. A plasma clearance study of injected

folic acid in six women taking oral contraceptives and seven controls was recently reported (42). Plasma concentrations measured 5 minutes after injection were significantly lower in the contraceptive users. After the initial 5 minutes there was no difference in clearance rates, suggesting that only the initial distribution volume or the initial tissue uptake was greater in the subjects on medication.

As mentioned earlier, plasma protein concentrations change during treatment with contraceptive steroids (15). About half of the folate in plasma is reported to be protein-bound (43), and some effects of oral contraceptive use on the binding of folic acid to blood proteins have been reported (44).

There has been little investigation of effects of contraceptive steroids on the tissue metabolism of folate. Bovine *et al.* (45) reported data indicating that oophorectomy resulted in decreased tetrahydrofolic acid and increased methyltetrahydrofolic acid in livers. This effect was partially corrected by exogenous estrogen treatment. It is not known whether contraceptive steroids given to normal women affect metabolic interconversions of various forms of endogenous folate. Another interesting postulate is that induction of drug metabolizing enzymes in the liver by exogenous chemicals may increase physiological demand for folate (46). At present, there are not sufficient data to decide whether derangements in folate metabolism unrelated to absorption occur in oral contraceptive users, and further research is needed.

Vitamin B_{12}. Vitamin B_{12} status in oral contraceptive users has received less attention than that of folate, possibly in part, because there have been no reported cases of megaloblastic anemia with evidence of B_{12}

deficiency in oral contraceptive users. All women with apparent folate deficiency anemia in association with use of oral contraceptives had normal serum B_{12} levels (38).

There are several reports (47, 48), however, that women using oral contraceptives have statistically significant lowering of serum B_{12} levels when compared to normal control women. Wertalik *et al.* (48) observed four women before and after starting oral contraception, and noted that all developed reductions in serum B_{12} levels, ranging from 24 to 58%. Reduction in B_{12} levels in women using oral contraceptives seldom appears to be severe and has not been associated with decreased tissue (red blood cell) B_{12}, anemia, or hypersegmentation of polymorphonuclear leukocytes (47, 48).

Some women taking oral contraceptives may have subnormal levels of both folate and B_{12}, suggesting a relationship between these two changes (48). However, when women with low serum folate and B_{12} concentrations were treated with oral folic acid and cyanocobalamin without stopping oral contraceptives, their serum folate levels rose, but serum B_{12} concentrations did not (48). Therefore, a clear relationship between B_{12} and folate serum concentrations in contraceptive users is not apparent.

African women using combined oral contraceptives were observed to have lower serum B_{12} levels than nonusers (47). However, a significant B_{12} reduction was not found in women given 'Depo-Provera' (Medroxyprogesterone acetate) every three months, possibly indicating that estrogens have a greater effect on B_{12} metabolism than do progestogens. The mechanism for an effect of any oral contraceptives on B_{12} is not clear.

Pyridoxine (Vitamin B_6). Pyridoxine status is most commonly assessed by measuring the amounts of xanthurenic acid and other tryptophan metabolites

in the urine. Most of these are excreted in increased amounts when B_6 is deficient. Excretion of those metabolites in some women taking oral contraceptives resembles that found in pyridoxine deficient women and can be corrected by giving large amounts of pyridoxine (49). This has suggested that oral contraceptives may either produce an absolute deficiency of pyridoxine or increase the body's requirement for this important vitamin.

Rose showed that excretion of the following was increased in women taking oral contraceptives: kynurenine, 3-hydroxykynurenic acid, acetylkynurenine, N'-methylnicotinamide; but not 2-pyridone (49, 50). Lack of elevation of 2-pyridone with oral contraceptive use may be due to interference by progestogens with the effects of estrogen on nicotinic acid metabolism, in particular the oxidation of N'-methylnicotinamide to 2-pyridone (52).

Urinary tryptophan metabolites appeared to increase with the dose of estrogenic component and with the duration of treatment (51). Estrogens given alone produce the same changes in urinary tryptophan metabolites of women as do estrogen-progestogen combination (50). Progestogens, in contrast, have been found not to produce these effects. There is evidence that estrogen administration results in increased activity of tryptophan pyrrolase.

A mestranol-norethynodrel combination has a greater stimulatory effect on tryptophan pyrrolase in rats than does estradiol, and progesterone alone is an inhibitor of this enzyme in rat liver (52). Estrogen may modify the activity of enzyme in the kynurenine pathway other than tryptophan pyrrolase. Mason and Manning (53) have presented in vitro and in vivo evidence that estrogens may affect binding of pyridoxal phosphate to the apoenzyme of

kynurenine transaminase.

Estrogens and progestogens may also affect steps in the tryptophan-niacin pathway after the formation of 3-hydroxyanthranilic acid. Hormones probably do not change tissues levels of nicotinamide adenine dinucleatide (NAD) in normal humans, but they may regulate how much NAD is derived from tryptophan (54).

A number of methods have been described for estimating vitamin B_6 compounds in blood and tissues (55). Pyridoxal phosphate (PLP) is a major form of vitamin B_6 in blood, and its level in blood has been shown to correlate with other biochemical indications of B_6 nutrition (55). Lumeng *et al.* (56) compared plasma PLP concentrations of women taking oral contraceptives for six months or more. They noted that PLP levels were lower in contraceptive users than nonusers, but this was less commonly found than was excretion in urine of abnormal quantities of tryptophan metabolites. This supports the idea that the abnormalities in tryptophan metabolism induced by contraceptive steroids do not always reflect absolute B_6 deficiency.

A recent study (57) of normal human plasma indicates that added PLP binds strongly to plasma proteins, especially albumin; that pyridoxal is more weakly bound; and that pyridoxine does not bind. Such information was suggested as a basis for investigating the possible modifying effects of exogenous steroids.

There is evidence that altered pyridoxine status may be associated with the mental depression that sometimes occurs in women taking oral contraceptives. According to Green and co-workers (58), an increased level of tryptophan oxygenase may result in a decreased availability of tryptophan for serotonin synthesis. Luhby (59) stated that depression may be related

to a decreased production of serotonin. Luhby also found that a minimal dose of about 25 mg. of pyridoxine hydrochloride is required to normalize xanthurenic acid excretion in oral contraceptive users. This amount of the vitamin is much greater than generally recommended daily allowances.

Vitamin A. Several reports have indicated that women taking oral contraceptives had significantly increased levels of vitamin A in serum or plasma (60, 61). The data of Yeung (60) demonstrate this clearly (Table 3). The existence of elevated levels of vitamin A for protracted periods has given rise to the concern that these levels may represent hypervitaminosis and, after pregnancy is decided upon, result in congenital abnormalities in newborn infants (61). The use of an intramuscular progestogen preparation 'Depo-Provera' every three months did not lead to an increase in the level of plasma vitamin A level (63).

Table 3: Mean fasting plasma vitamin A levels in women during the menstrual cycle (60)

Days of cycle	Mean values (μg ± SD per 100 ml)		*p* value for significance of difference between values in columns 2 & 3
	Controls	Woman taking oral contraceptives	
1-5	27.3 ± 0.9	45.6 ± 4.3	<0.01
6-10	33.9 ± 1.4	40.6 ± 3.2	<0.05
14-19	32.3 ± 1.0	46.5 ± 4.5	<0.01
20-24	29.3 ± 0.7	45.4 ± 4.7	<0.01
25-28	30.5 ± 1.1	42.6 ± 2.3	<0.01
Total cycle	30.5 ± 5.0	44.2 ± 14.5	<0.01

Briggs and co-workers (62) have verified that combination-type oral contraceptives may elevate the plasma level of vitamin A, while Medroxyprogesterone acetate had the opposite effect. Vitamin A exists in plasma mainly bound to beta lipoproteins. As this lipid fraction is increased during treatment with estrogen-containing oral contraceptive, those authors believed that the increase in plasma level of vitamin A was secondary to alterations of the plasma lipids.

Ascorbic acid. The effects of oral contraceptives on ascorbate levels in plasma, leukocytes and platelets of African women living in the Republic of Zambia have been studied in some detail by Briggs and Briggs (63, 64). They concluded that administration of oral contraceptives leads to ascorbate decreases in the plasma, leukocytes and platelet concentrations (Table 4).

Table 4: Effect of oral contraceptives on concentration (±1 SD) of ascorbic acid.

	Control	Oral Contraceptives	Reference
Platelets (mg/g wet wt.)	0.26 ± 0.11	0.19 ± 0.13[a]	(64)
white cells ($\mu g/10^8$ cells)	39 ± 28	26 ± 22	(64)
Plasma (mg/100 ml.)	0.75 ± 0.2	0.45 ± 0.31	(63)

[a] p value is <0.01

A more detailed study of the effect of oral contraceptives on the ascorbic acid level in leukocytes was submitted by McLeroy and Achendal (65). The results obtained are shown in Table 5. The concentration of ascorbic acid was significantly decreased as the result of administering the

contraceptive agents, and it may be noted that the level in those subjects on contraceptives and taking ascorbic acid supplements was no higher than in those on the ordinary intake.

Table 5: Effect of oral contraceptives and vitamin C supplementation on the concentrations of ascorbic acid (mg/100g) in the leukocytes of mature women (65).

Measure & group	Control	Experimental
Dietary intake of ascorbic acid, mg/day		
All subjects	86 ± 45	84 ± 48
Ascorbic acid, mg/100 g leukocytes		
All subjects	25.7 ± 14.5	19.0 ± 6.6[a]
No vitamin C supplement	24.1 ± 14.5	19.0 ± 7.0[b]
With vitamin C supplement	35.2 ± 12.1[c]	19.4 ± 6.1[a]

[a] Significantly lower ($p<0.01$) with respect to controls.

[b] Significantly lower ($p<0.05$) with respect to controls.

[c] Significantly higher ($p<0.05$) with respects to groups of all subjects or subjects on ordinary dietary intake.

Thiamine. There appears to be only one reference on the effect of oral contraceptives on thiamine. Briggs and Briggs (66) studied 20 healthy women consuming normal mixed diets. None of the women took vitamin supplements. They were given combined oral contraceptives during menstrual cycles. Before treatment, the erythrocyte transketolase activity was stimulated by excess thiamine pyrophosphate. After the third cycle, the stimulation was significantly greater than during the control period. This indicated that a relative deficiency of thiamine is sometimes induced by contraceptive

steroid combinations. More investigation of their effects on thiamine metabolism is needed.

Riboflavin. Employing the activity of erythrocyte glutathione reductase as an indicator of riboflavin nutrition, Spanitak and co-worker (67) found that the activity was significantly lower than normal in the erythrocytes of women taking oral contraceptives. They also observed that the in vitro stimulation of erythrocyte glutathione reductase activity by the addition of flavin-adenine dinucleotide (FAD) to the assay mixture was much less for the control women than for those taking contraceptives. Briggs and Briggs (63) have reported that the urinary excretion of riboflavin was decreased markedly in 10 African women taking combined contraceptives.

Niacin. As mentioned earlier, estrogens induce increased activity of the enzyme that convert tryptophan to niacin (49), and also an increase in the basal excretion of N'-methylnicotinamide, a nicotinic acid metabolite, in women taking oral contraceptives (50). Increasing the yield of niacin from tryptophan may decrease the need for preformed dietary niacin.

Vitamin E (Tocopherol). Oral contraceptives and tocopherol relationships in female rats have been explored in some detail by Aftergood and co-worker (68). In rats receiving oral contraceptives, the plasma tocopherol concentration at the end of a 28-day period was significantly lower than in the control rats. In the only reported study of humans, Briggs and Briggs (63) showed that the plasma tocopherol concentration of oral contraceptive users was not significantly lower than for the controls. Oral contraceptives, therefore, may lower alpha-tocopherol plasma concentrations in rats but an effect on human alpha-tocopherol metabolism has not been demonstrated.

Vitamin K. Increased serum levels of vitamin K-dependent clotting factors have been found in women taking oral contraceptives (69). Schrogie (70) found that women receiving oral contraceptives had a smaller than normal level of anti-coagulant coumarin, a vitamin K antagonist. These observations suggest that the need for vitamin K is reduced by oral contraceptives.

The risk of thromboses occurring as a side effect of oral contraceptives has been studied by a number of researchers. Tyler (71) concluded that no evidence was available to relate spontaneous intravascular clotting with the use of 'Enovid', a combined oral contraceptive. Later, the Food and Drug Administration also found that there was no significant increase in the risk of thromboembolic incidence from the use of this agent (72). Vessey (73) believed that oral contraceptives are a cause of venous thromboembolism and cerebral thrombosis, yet he did not indicate that they are a cause of coronary thrombosis. Inman (74) pointed out a positive correlation between the dose of estrogen and the risk of coronary thrombosis.

EFFECT OF ORAL CONTRACEPTIVES ON MINERAL FUNCTIONS

Iron. Oral contraceptives result in a significant reduction of the menstrual blood losses (75). So it could be expected that the incidence of iron deficiency anemia would decrease in women using oral contraceptives. However, there is no significant increase of the hemoglobin concentration during oral contraceptive therapy (75, 76). This may be because the plasma volume increases relatively more than the red cell mass. Serum iron concentration also increases and this increase does not appear to be related to the decrease attributed to menstrual losses (75).

Jacobi and Goffney reported that plasma iron concentration and total iron binding capacity (TIBC) increase during oral contraceptive therapy. Cause of the increase in plasma iron concentration is probably an increased mobilization of iron from stores, mediated by the elevated transferrin concentration, which is probably due to an increase in protein synthesis (77). The changes in levels of serum iron and TIBC do not appear to be inter-dependent and are controlled separately (78).

No significant difference was found by Mardell in the effect of different types oral contraceptive preparations on TIBC. The serum iron concentration tended to be higher when the preparation contained progesterone (78). However, Briggs found that oral progestogen stimulated an increase in both serum iron and TIBC (79). On the other hand, Powell *et al.* (80) found contrasting results by giving Medroxyprogesterone acetate, a pure progestational agent, to 30 women. Eighteen of these women had previously taken oral contraceptive of the combined estrogen-progestogen type and during that time, their serum iron levels were raised. After Medroxyprogesterone acetate was injected, the levels fell significantly (Figure 6). In a further study of 12 postpartum women, the serum levels did not change significantly after Medroxyprogesterone acetate (Figure 7). These observations suggested that oral progestogen has no effect on the serum levels of iron, TIBC and transferrin (80).

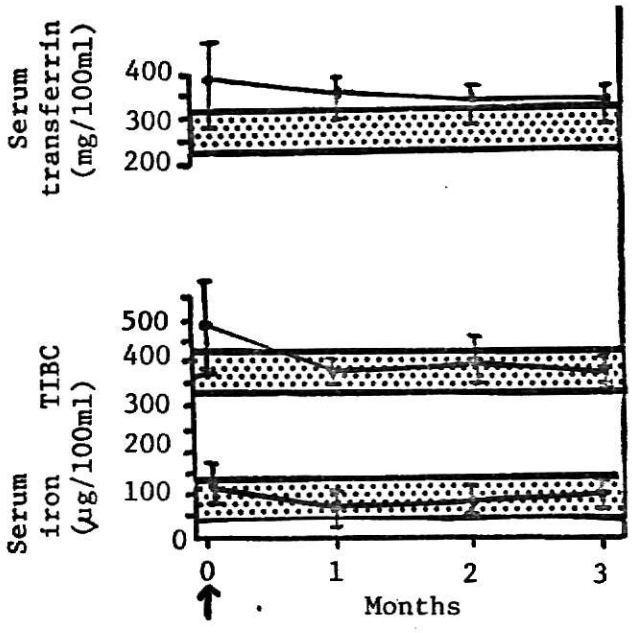

Figure 6. Serum iron levels in 18 women (means ± S.D.) At the point marked the arrow oral contraceptives were stopped and the subjects received an injection of Medroxyprogesterone acetate. Shaded areas indicate normal means ± S.D. (80)

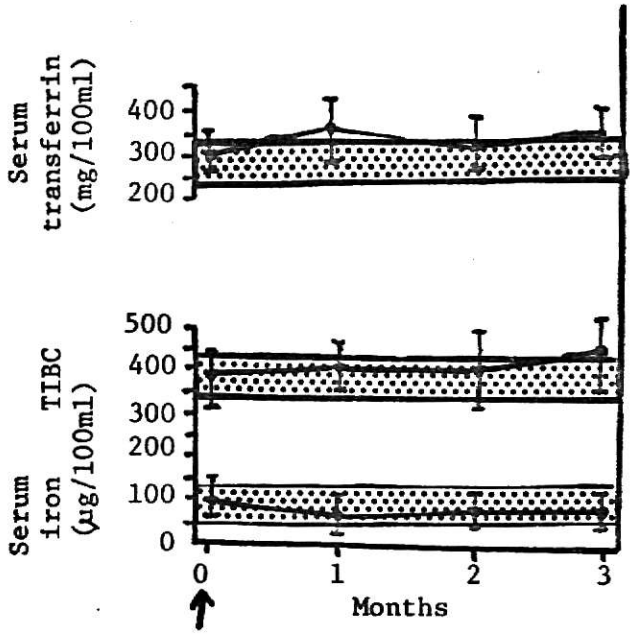

Figure 7. Serum iron levels in 12 post-partum women who received Medroxyprogesterone acetate intramuscularly at the point indicated by the arrow. Shaded areas indicate normal means ± S.D. (80)

Copper. The copper content of maternal blood increases during the later stages of gestation. Following the administration of oral contraceptive, serum copper concentration is elevated (81). The green copper-carrying protein, ceruloplasmin, also is increased by estrogen (82). Schenker *et al.* (83) found that the rise of serum copper content in oral contraceptive users is not due to the estrogenic compound alone, but that the progestive agents also play a part.

The increases in ceruloplasmin and blood copper levels point to increased absorption of dietary copper and consequently, less chance of dietary copper inadequacy. In addition, increased ceruloplasmin and blood copper levels suggest that the need for vitamin A and ascorbic acid may be altered by oral contraceptives (2).

Zinc. Halsted *et al.* (84) reported that women taking oral contraceptive had significantly lower plasma zinc levels. This may be caused by a shift of plasma zinc into the erythrocyte. Differences occur between the various estrogen-progestin combinations in the serum zinc levels. Schenker *et al.* (83) pointed out that the zinc mean values were lower with the sequential type oral contraceptives than with the combined. McBean *et al.* (85) concluded that estrogen significantly lowered plasma zinc concentration in rats when compared with the control group. In contrast, progesterone did not significantly decrease plasma zinc.

However, O'Leary and Spellacy (86) showed that zinc levels were not significantly lowered in pregnant women, but they were elevated in subjects taking oral contraceptives. Halsted *et al.* (84) argued that the technique Spellacy used in respect to collection and preparation of samples provided a strong probability of contamination.

Calcium. Caniggia *et al.* (87) administered an oral estrogen-progestogen combination to 15 post-menopausal women for six months. Comparing intestinal absorption of radio calcium before and after oral contraceptive treatment, they concluded that the estrogen in the oral contraceptive significantly improved intestinal absorption of calcium. The stimulation of calcium absorption by oral contraceptive should be beneficial since the average calcium intake for women in the United States is much less than the Recommended Dietary Allowances (2).

Magnesium. It has been reported that during oral contraceptive therapy, serum levels of magnesium are decreased, due to estrogen inhibition of bone resorption (88). There is some evidence that magnesium may be involved in vascular health and blood coagulation. Women taking 'Enovid' showed a decreased clotting-time (89). It appeared that the protective value of the female endocrine system against the development of early cardiovascular atherosclerotic disease may be seriously impaired by the use of oral contraceptives.

Thin (90) studied the magnesium levels in women with normal menstrual cycles and women who used oral contraceptive. Neither menstruation nor oral contraceptive usage appeared to have any effect on plasma magnesium. Thin stated that this may be due to the lower dosage of estrogen in the oral contraceptive compared with the other research.

FURTHER ADVANCES IN BIRTH CONTROL

Metabolic changes that occur in oral contraceptive users are attributed to the estrogen component of the oral contraceptive. 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 (91). Results demonstrated that this 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. An advantage over oral contraceptive appears to be the freedom from the necessity to remember to take medication daily. Following discontinuation of therapy, fertility returned to normal (91).

One type of oral contraceptive which contains only progesterone is the 'mini' pill which is ingested each day (92). Nelson (92) studied the effect of the 'mini' pill on 342 women. He found general acceptance of the pill to be good. Side effects other than menstrual irregularity were rare. Without the estrogen component, the usual oral contraceptive side effects such as nausea, weight gain, fluid retention, hypertension, and alteration of carbohydrate metabolism were not observed.

The recent development in family planning is the introduction of an ultra-low-dose combined oral contraceptive containing only 30 μg.of Ethinyl estradiol plus 150 μg. of d-Norgestrel (93). This product is highly effective in protecting against pregnancy and is associated with a very low incidence of undesirable side effects. Clinical studies on this product showed no change in body weight, unaltered blood pressure, and little or no depression. The only adverse side effect was an increase in intramenstrual bleeding which is usually mild and almost entirely confined to early cycles of treatment (93). The conception rate of these newer methods is slightly higher than with the estrogen-progestogen combinations, but they appear to have advantages at least for some women.

SUMMARY

Oral contraceptives have gained wide acceptance in the United States because of their effectiveness and convenience for fertility control. Available oral contraceptives are composed of estrogen and progestin in various dosages. All oral contraceptives fall into three major regimens: combined; sequential; and continuous progestin.

Contraceptive steroids seem to alter the metabolism of every nutrient tested so far. Most of these changes are attributed to the estrogen component of the oral contraceptive. This report relates the findings of current research on the effects of oral contraceptives to nutrition.

There is evidence that metabolism of proteins, carbohydrates and lipids is altered by oral contraceptives. Plasma albumin is decreased and the alpha and beta globulin and fibrinogen are increased with oral contraceptive use. Finding no increase in urinary nitrogen suggests that there is increased utilization of amino acids. Tryptophan metabolism is altered by oral contraceptive use. Estrogens often result in small elevations in blood glucose and plasma insulin levels which is evidence of altered carbohydrate metabolism. The estrogenic component of the pill appears to increase plasma triglyceride levels markedly, but there are no consistent changes in plasma cholesterol and often they are related to age.

Oral contraceptives alter the requirements for various vitamins. Biochemical and clinical findings point to an increased need for vitamin B_6 (pyridoxine) by women using oral contraceptive, since pyridoxal phosphate is required as a coenzyme for the conversion of tryptophan to niacin. The need for riboflavin also increases, since it is involved in the conversion

of pyridoxine phosphate to the metabolically active form, pyridoxal phosphate. The absorption of polyglutamic folic acid, the major food form of folic acid, is substantially impaired in women receiving oral contraceptive, and folic acid deficiency has been reported. Serum B_{12} binding capacity has been found to increase during oral contraceptive therapy. Decreased serum B_{12} values have also been found in women on oral contraceptive. Plasma concentration of vitamin A is elevated; this suggests that vitamin A needs may be decreased during oral contraceptive use. The concentration of ascorbic acid in plasma and blood corpuscles is reduced in women on oral contraceptive. Increased serum levels of vitamin K-dependent clotting factors have been found in women taking oral contraceptive. This suggests that vitamin K may be needed in lesser amounts by oral contraceptive users.

Oral contraceptive use also alters the requirements for various minerals. Most studies show that oral contraceptives cause an increase in serum iron and copper and a decrease in plasma zinc. The transport proteins for iron and copper (transferrin and ceruloplasmin) increase in the serum prior to the mineral changes, suggesting that they induce the alterations. The decrease in plasma zinc may be caused by a shift of plasma zinc into the erythrocyte. Intestinal absorption of calcium is improved significantly during oral contraceptive use; this should be beneficial to most women in the United States, since their calcium intake is low. Serum levels of magnesium are decreased, due to estrogen inhibition of bone resorption.

Although a majority of women are able to take combined oral contraceptive without very serious side effects, alterations of metabolism appear to be caused mainly by the estrogen component. Injection of progestin and the use

of low-dose combined oral contraceptive provide less reliable contraception but cause fewer metabolic alterations.

Whether 'the pill' changes the nutritional requirements of the women-users cannot be answered from the existing data. One can conclude that no large increases in requirements occur, because virtually no clinical signs of nutritional deficiency have been noted. The best advice for a woman taking the pill is to eat a healthful, well-balanced diet which provides the recommended allowance for all nutrients.

REFERENCES

1. Mishell, D.R.: Current status of contraceptive steroids and the intrauterine device. Clin. Obstet. Gynec. 17:35, 1974.

2. Theuer, R.C.: Effect of oral contraceptive agents on vitamins and mineral needs: a review. J. Repro. Med. 8:13, 1972.

3. Cleary, R.E., and Dajani, R.M.: Current status of oral contraceptives. Med. Clin. N. Amer. 54:163, 1970.

4. Drill, V.A.: Endocrine properties of oral contraceptives. Metabolism 14:295, 1965.

5. Foss, G.L., Svendsen, E.K., Fotherby, K., and Richard, D.J.: Contraceptive action of continuous low dose of norgestrel. Brit. Med. J. 4:489, 1968.

6. Saunders, F.J.: Endocrine properties and mechanism of action of oral contraceptives. Federation Proc. 29:124, 1970.

7. Cargille, C.M., and Ross, G.T.: Oral contraceptives and follicle stimulating hormone. Lancet 1:924, 1968.

8. Bowman, J.A.: The effect of norethindrone-mestranol on cervical mucus. Am. J. Obstet. Gynec. 102:1039, 1968.

9. Craft, I.L., and Wise, I.: Oral contraceptive and plasma amino acid. Nature 222:487, 1969.

10. Horne, C.H.W., Howie, P.W., Weri, R.J., and Goudie, R.B.: Effect of combined estrogen-progestogen oral contraceptives on serum levels of alpha-2-macroglobulin, transferrin, albumin and Immunoglobulin G. Lancet 1:49, 1970.

11. Spellacy, W.M.: Metabolic effects of oral contraceptives. Alin. Obstet. Gynec. 17:53, 1974.

12. Poller, L., and Thomson, J.M.: Sequential oral contraception and clotting factors. Brit. Med. J. 2:822, 1969.

13. Briggs, M., and Briggs, M.: Effects of some contraceptive steroids on serum protein of women. Biochem. Pharmacol. 22:2277, 1973.

14. Rose, D.P., and Braidman, I.P.: Oral contraceptive, depression, amino acid metabolism. Lancet 1:1117, 1970.

15. Elstein, M.: Oral contraceptive and serum proteins. Lancet 1:367, 1970.

16. Kalesh, D.G.: Effect of estrogen-containing oral contraceptives on platelet and plasma amino acid concentration. Contraception 4:183, 1971.

17. Rooks, W.H.,II, Kugler, S.L., and Dorfman, R.I.: The relative expressed estrogenicity of oral contraceptives. Fertil. & Steril. 19:419, 1968.

18. Spellacy, W.N., Buhi, W.C., and Birk, S.A.: The effect of estrogen on carbohydrate metabolism. Am. J. Obstet. Gynec. 114:378, 1972.

19. Goldman, J.A., Ovadia, J.L., and Eckerling, B.: Effect of progesterone on glucose tolerance in women. Israel J. Med. Sci. 4:878, 1968.

20. Spellacy, W.M., McLeod, A.G.W., and Buhi, W.C.: Medroxyprogesterone acetate and carbohydrate metabolism: Measurement of glucose, insulin and growth hormone during 6 months time. Fertil. & Steril. 21:457, 1970.

21. Larsson-Cohn, U., Tengstrom, B., and Wide, L.: Glucose tolerance and insulin response during daily continuous low-dose oral contraceptives treatment. Acta. Endocrinol. 62:242, 1969.

22. Spellacy, W.M., Buhi, W.C., and Birk, S.A.: The effect of the progestogen ethynodiol diacetate on glucose, insulin and growth hormone after 6 months treatment. Acta Endocrinol. 70:373, 1972.

23. Spellacy, W.M.: Carbohydrate metabolism in male infertility and female fertility-control patients. Fertil. & Steril. 27:1132, 1976.

24. Starup, J., Date, J., and Deckert, T.: Serum insulin and intravenous glucose tolerance in contraception. Acta Endocrinol. 58:527, 1968.

25. Spellacy, W.M.: A review of carbohydrate metabolism and the oral contraceptives. Am. J. Obstet. Gynec. 104:448, 1969.

26. Spellacy, W.M.: Cross-sectional investigation of carbohydrate metabolism in women taking sequential or combination type oral contraceptives: measurement of blood glucose, plain insulin, and plasma growth hormone during an oral glucose tolerance test. Southern Med. J. 63:152, 1970.

27. Wynn, V., and Doar, J.W.H.: Some effects of oral contraceptives on serum-lipid and lipoprotein levels. Lancet 2:720, 1966.

28. Phillips, N., and Duffy, T.: One-hour glucose tolerance in relation to the use of contraceptive drugs. Am. J. Obstet. Gynec. 116:91, 1973.

29. Furman, R.H., Alaupovic, P., and Howard, R.P.: Effects of androgens and estrogens on serum lipids and the composition and concentration of serum lipoproteins in normolipemic and hyperlipemic states. Prog. Biochem. Pharmacol. 2:215, 1967.

30. Gustafson, A., and Svanborg, A.: Gonadal steroid effects on plasma lipoproteins and individual phospholipids. J. Clin. Endocrinol. 35:203, 1972.

31. Glueck, C.J., Levy, R.I., and Fredrickson, D.S.: Norethindrone acetate, postheparin lipolytic activity, and plasma triglycerides in familial types I, III, IV and V hyperlipoproteinemia. Ann. Intern. Med. 75:345, 1971.

32. Barton, G.M.G.: Oral contraceptives and serum lipids. Am. J. Obstet. Gynec. Brit. Comm. 77:551, 1970.

33. Stokes,T., and Wynn, V.: Serum lipids in women on oral contraceptives. Lancet 2:677, 1971.

34. Hazzard, W.R.: Studies on the mechanism of increased plasma triglyceride levels induced by oral contraceptives. New England J. Med. 280:471, 1969.

35. Kekki, M., and Nikkila, E.A.: Plasma triglyceride turnover during use of oral contraceptives. Metabolism 20:878, 1971.

36. Aitken, J.M., Lorimer, A.R., and Mckory, H.D.: The effects of oophorectomy and long-term mestranol therapy on the serum lipids of middle-aged women. Clin. Sci. 41:597, 1971.

37. Shojania, A.M., Hornady, G., and Barnes, P.H.: Oral contraceptives and serum folate level. Lancet 1:1376, 1968.

38. Streiff, R.R.: Folate deficiency and oral contraceptives. J. Am. Med. Ass. 214:105, 1970.

39. Stephens, M.E.M., Craft, I., Peters, T.J., and Hoffbrand, A.V.: Oral contraceptives and folate metabolism. Clin. Sci. 42:405, 1972.

40. Spray, G.H.: Oral contraceptives and serum folate levels. Lancet 2:110, 1968.

41. Shojania, A.M., Hornady, G., and Narnes, P.H.: The effect of oral contraceptives on folate metabolism. Am. J. Obstet. Gynec. 111:782, 1971.

42. Shojania, A.M., Hornady, G.J., and Scaletta, D.: The effect of oral contraceptives on folate metabolism III. Plasma clearance and urinary folate excretion. J. Lab. Clin. Med. 85:185, 1975.

43. Markkanen, T., Virtanen, S., Himanen, P., and Pajula, R.L.: Transferrin. the third carrier protein of folic acid activity in human serum. Acta Haematol. 48:213, 1972.

44. Markkanen, T., Himanen, P., Pajula, R.L., Ruponene, S., and Castren, O.: Binding of folic acid to serum protein. I. The effect of pregnancy. Acta Haematol. 50:85, 1973.

45. Bovina, C., Tolomalli, B., Rovinetti, C., and Marchetti, M.: Effect of estradiol on folate coenzymes in the rat. Int. J. Vitam. Nutr. Res. 41:453, 1971.

46. Maxwell, J.D., Hunter, J., Stewart, D.A., Ardeman, S., and Williams, R.: Folate deficiency after anticonvulsant drugs: an effect of hepatic enzyme induction? Brit. Med. J. 1:297, 1972.

47. Briggs, M., and Briggs, M.: Endrcrine effects on serum vitamin B_{12}. Lancet 2:1037, 1972.

48. Wertalik, L.F., Metz, E.N., LoBuglio, A.F., and Balcerzak, S.P.: Decreased serum B_{12} levels with oral contraceptive use. J. Am. Med. Ass. 221:1371, 1972.

49. Rose, D.P.: Excretion of xanthruenic acid in urine of women taking progestogen-estrogen preparations. Nature 210:196, 1966.

50. Rose, D.P.: The influence of estrogens on tryptophan metabolism in man. Clin. Sci. 31:265, 1966.

51. Rose, D.P., and Adams, P.W.: Oral contraceptives and tryptophan metabolism. Effects of estrogen in low dose combined with a progestogen and of a low-dose progestogen given alone. J. Clin. Pathol. 25:252, 1972.

52. Rose, D.P., and McGinty, F.: The effect of steroid hormones on tryptophan metabolism. Adv. Steroid Biochem. Pharmacol. 1:97, 1970.

53. Mason, M., and Manning, B.: Effects of steroid conjugates on availability of pyridoxal phosphate for kynureninase and kynurenine aminotransferase activity. Am. J. Clin. Nutr. 24:786, 1971.

54. Wolf, H.: Hormonal alteration of efficiency of conversion of tryptophan to urinary metabolites of niacin in man. Am. J. Clin. Nutr. 24:792, 1971.

55. Hamfelt, A.: Pyridoxal phosphate concentration and amino-transferase activity in human blood cells. Clin. Chim. Acta. 16:19, 1967.

56. Lumeng, C., Cleary, R.E., and Li, T.K.: Effect of oral contraceptives on the plasma concentration of pyridoxal phosphate. Am. J. Clin. Nutr. 27: 326, 1974.

57. Anderson, B.B., Newmark, P.A., Rawlins, M., and Green, R.: Plasma binding of vitamin B_6 compounds. Nature 250:502, 1974.

58. Green, A.R., Joseph, M.H., and Gurzon, G.: Oral contraceptives, depression, and amino acid metabolism. Lancet 1:1288, 1970.

59. Luhby, A.L.: Pyridoxine and oral contraceptives. Lancet 2:1083, 1970.

60. Yeung, D.L.: Effects of oral contraceptives on vitamin A metabolism in the human and the rat. Am. J. Clin. Nutr. 27:125, 1974.

61. Wild, J., Schorah, C.J., and Smithells, R.W.: Vitamin A, pregnancy and oral contraceptives. Brit. Med. J. 1:57, 1974.

62. Briggs, M., Briggs, M., and Bennum, M.: Steroid contraceptive and plasma carotenoids. Contraception 6:275, 1972.

63. Briggs, M., and Briggs, M.: Oral contraceptives and vitamin nutrition. Lancet, 1:1234, 1974.

64. Briggs, M., and Briggs, M.: Vitamin C requirements and oral contraceptives. Nature 238:277, 1972.

65. McLeroy, V.J., and Schendal, H.E.: Influence of oral contraceptives on ascorbic acid concentrations in healthy, sexually mature women. Am. J. Clin. Nutr. 26:191, 1973.

66. Briggs, M., and Briggs, M.: Thiamine status and oral contraceptives. Contraception 11:151, 1975.

67. Sanpitak, N., and Chayntimonkul, L.: Oral contraceptives and riboflavin nutrition. Lancet 1:836, 1974.

68. Aftergood, L., and Alfin-Slater, R.B.: Oral contraceptive-alpha-tocopherol interrelationships. Lipids 9:91, 1974.

69. Egeberg, O., and Owren, P.A.: Contraception and blood coagulability. Brit. Med. J. 1:220, 1963.

70. Schrogie, J.L.: Effect of oral contraceptive on vitamin K-dependent clotting activity. Clin. Pharmacol. Therap. 8:670, 1967.

71. Tyler, E.T.: Oral contraceptive and venous thrombosis. J. Am. Med. Ass. 185:131, 1963.

72. Editorial. FDA report on Enovid. J. Am. Med. Ass. 185:776, 1963.

73. Vessey, M.P., and Doll, R.: Investigation of relationship between use of oral contraceptive and thromboembolic disease. A further report. Brit. Med. J. 2:651, 1969.

74. Inman, W.H.W., Vessey, M.P., Westerholm, B., and Engelund, A.: Thromboembolic disease and the steroidal content of oral contraceptive. Brit. Med. J. 2:203, 1970.

75. Norrby, A., Rybo, G., and Solvell, L.: The influence of a combined oral contraceptive on the absorption of iron. Scand. J. Haemat. 9:43, 1972.

76. Burton, J.L.: Effect of oral contraceptive on hemoglobin, packed-cell volume, serum-iron and total iron-binding capacity in healthy women. Lancet 1:978, 1967.

77. Jacobi, J.M., and Gaffney, T.J.: Immunochemical quantitative of human transferrin in pregnancy and during the administration of oral contraceptive. Brit. J. Haemat. 17:503, 1969.

78. Mardell, M.: A comparison of the effect of oral contraceptive, pregnancy and sex on iron metabolism. J. Clin. Endocrinol. Metab. 29:1489, 1969.

79. Briggs, M., and Briggs, M.: Contraceptives and serum proteins. Brit. Med. J. 3:521, 1970.

80. Powell, L.W., Jacobi, J.M., Gaffney, T.J., and Adam, R.: Failure of a pure progestogen contraceptive to affect serum levels of iron, transferrin, protein-bound iodine, and transaminase. Brit. Med. J. 3:194, 1970.

81. Mckenzie, J.M.: Influence of oral contraceptive on serum zinc and copper concentration. Federation Proc. 33:692, 1974.

82. Tovey, L.A.D., and Latha, G.H.: Ceruloplasmin and green plasma in women taking oral contraceptive, in pregnant women and in patient with rheumatoid arthritis. Lancet 2:596, 1968.

83. Schenker, J.G., Hellerstein, S., Jungreis, E., and Polishuk, W.Z.: Serum copper and zinc levels in patients taking oral contraceptive. Fertil. Steril. 22:229, 1971.

84. Halsted, J.A., Smith, J.C., Hackley, B.M., and McBean, L.: Plasma zinc and copper levels. Am. J. Obstet. & Gycerol. 105:645, 1969.

85. McBean, L.D., Smith, J.C., and Halsted, J.A.: Effect of oral contraceptive hormones on zinc metabolism in the rat. Federation Proc. 30:644, 1971.

86. O'Leary, J.A., and Spellacy, W.M.: Zinc and copper levels in pregnant women and those taking oral contraceptive. Am. J. Obstet. & Gyncol. 103:131, 1969.

87. Caniggia, A., Gennari, C., Borrello, G., and Bencini, M.: Intestinal absorption of Ca-47 after treatment with oral estrogen-progestogen in senile osteoporosis. Brit. Med. J. 4:30, 1970.

88. Goldsmith, N.F., Pace, N., Baumberger, J.P., and Ury, H.: Magnesium and citrate du ing the menstrual cycle: effect of an oral contraceptive on serum magnesium. Fertil. Steril. 21:292, 1970.

89. Lowenstein, F.: Oral contraceptive and cardiovascular disease. Lancet 2:1365, 1966.

90. Thin, C.G.: The effect of an oral contraceptive agent on the concentrations of calcium and magnesium in plasma, erythrocytes and platelets in women. Ann. Clin. Res. 3:103, 1971.

91. Schwallie, P.C., and Assenzo, J.R.: Contraceptive use-efficacy study using Medroxyprogesterone acetate administered as an intramuscular injection every 90 days. Fertil. & Steril. 24:331, 1973.

92. Nelson, J.H.: The use of the mini pill in private practice. J. Reprod. Med. 10:139, 1973.

93. Briggs, M.: Promoting the pill. Med. J. Aust. 1:242, 1976.

NUTRITION DURING ORAL CONTRACEPTIVE TREATMENT

by

ANNIE CHI-YEE SIU

B.S., MISSISSIPPI UNIVERSITY FOR WOMEN, 1975.

AN ABSTRACT OF A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods & Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1977

Oral contraceptives have gained wide acceptance in the United States because of their effectiveness and convenience for fertility control. Available oral contraceptives are composed of estrogen and progestin in various dosages. All oral contraceptives fall into three major regimens: combined; sequential; and continuous progestin.

Contraceptive steroids seem to alter the metabolism of every nutrient tested so far. Most of these changes are attributed to the estrogen component of the oral contraceptive. This report relates the findings of current research on the effects of oral contraceptives to nutrition.

There is evidence that metabolism of proteins, carbohydrates and lipids is altered by oral contraceptives. Plasma albumin is decreased and the alpha and beta globulin and fibrinogen are increased with oral contraceptive use. Finding no increase in urinary nitrogen suggests that there is increased utilization of amino acids. Tryptophan metabolism is altered by oral contraceptive use. Estrogens often result in small elevations in blood glucose and plasma insulin levels which is evidence of altered carbohydrate metabolism. The estrogenic component of the pill appears to increase plasma triglyceride levels markedly, but there are no consistent changes in plasma cholesterol and often they are related to age.

Oral contraceptives alter the requirements for various vitamins. Biochemical and clinical findings point to an increased need for vitamin B_6 (pyridoxine) by women using oral contraceptive, since pyridoxal phosphate is required as a coenzyme for the conversion of tryptophan to niacin. The need for riboflavin also increases, since it is involved in the conversion of pyridoxine phosphate to the metabolically active form, pyridoxal phosphate. The absorption of polyglutamic folic acid, the major food form of folic

acid, is substantially impaired in women receiving oral contraceptive, and folic acid deficiency has been reported. Serum B_{12} binding capacity has been found to increase during oral contraceptive therapy. Decreased serum B_{12} values have also been found in women on oral contraceptive. Plasma concentration of vitamin A is elevated; this suggests that vitamin A needs may be decreased during oral contraceptive use. The concentration of ascorbic acid in plasma and blood corpuscles is reduced in women on oral contraceptive. Increased serum levels of vitamin K-dependent clotting factors have been found in women taking oral contraceptive. This suggests that vitamin K may be needed in lesser amounts by oral contraceptive users.

Oral contraceptive use also alters the requirements for various minerals. Most studies show that oral contracéptives cause an increase in serum iron and copper and a decrease in plasma zinc. The transport proteins for iron and copper (transferrin and ceruloplasmin) increase in the serum prior to the mineral changes, suggesting that they induce the alterations. The decrease in plasma zinc may be caused by a shift of plasma zinc into the erythrocyte. Intestinal absorption of calcium is improved significantly during oral contraceptive use; this should be beneficial to most women in the United States, since their calcium intake is low. Serum levels of magnesium are decreased, due to estrogen inhibition of bone resorption.

Although a majority of women are able to take combined oral contraceptive without very serious side effects, alterations of metabolism appear to be caused mainly by the estrogen component. Injection of progestin and the use of low-dose combined oral contraceptive provide less reliable contraception but cause fewer metabolic alterations.

Whether 'the pill' changes the nutritional requirements of the women-users cannot be answered from the existing data. One can conclude that no large increases in requirements occur, because virtually no clinical signs of nutritional deficiency have been noted. The best advice for a woman taking the pill is to eat a healthful, well-balanced diet which provides the recommended allowance for all nutrients.