ORAL CONTRACEPTIVE STEROIDS AND CARBOHYDRATE METABOLISM
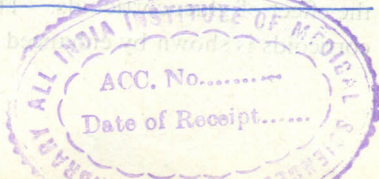
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There are a number of reports on metabolic alterations produced in patients receiving contraceptive pills. Alteration in thyroid function tests such as elevation of protein bound iodine (PBI), thyroid binding globulins (TBG) (6, 19) and a decrease in red blood cell uptake of radioactive tri-iodothyronin (11) has been shown to occur during oral contraceptive therapy. An increase in measurable total plasma corticoids in patients taking pills has also been shown (16). All these effects are also reported to occur during normal pregnancy presumably as a result of oestrogen excess. Alterations in carbohydrate metabolism in women receiving oral contraceptives have been less extensively investigated. Most studies on carbohydrate metabolism are not properly controlled. The results are therefore conflicting. Some investigators have reported "no change" while others have reported "marked alterations" in glucose tolerance (9, 10, 22).

Glucose Tolerance and the Pill

Gershberg *et al* in 1964 (10) were the first to report on the effect of oral contraceptives on carbohydrate metabolism and observed that a high percentage of women receiving 5 *mg* of nor-ethynodrel with mestranol in cyclic fashion for contraception had a decreased oral glucose tolerance. Wynn and Doar (33) studied intravenous and oral glucose tolerance in women receiving oral contraceptives for thirty days and found that while intravenous tolerance was normal, the oral glucose tolerance was abnormal. He suggested that effect of oestrogen was in some way due to a change in glucose absorption rather than to any diabetogenic activity. These workers also found that effect of intravenous hydrocortisone on glucose tolerance which was clearly evident before oral contraceptive treatment became much less impressive or was almost absent after oestrogen therapy. Spellacy *et al* (25) in 1966 investigated intravenous glucose tolerance and plasma insulin level before and after one cycle of oral Enovid and reported higher values of both glucose and insulin for the group receiving the contraceptive steroids. These workers later in 1967 reported normal glucose tolerance for all subjects receiving contraceptive steroids (27).

Patterson 1966 (18) reported thirty seven percent incidence of abnormal glucose tole[r]ance in women taking oral contraceptives for three months to seven years. Ten of thes[e] subjects with abnormal curve continued on oral contraceptive therapy for one more year. Fiv[e] of them became normal inspite of continued therapy while one showed further deterioration[.] He further reported that there is a higher incidence of abnormal glucose tolerance (56%) i[n] patients with a family history of diabetes than in those in whom there was no family histor[y] of diabetes. Wynn and Doar (33) made similar observations and also showed that there wa[s] an increase in serum free fatty acids and a delayed fall after glucose administration. The mos[t] striking observation was an increase in the levels of pyruvic acid in fasting state as well a[s] after glucose load. Recently Clinch et al (4) reported that a very low concentration of con[-]traceptive steroids significantly improved glucose tolerance, while stronger preparations cause[d] some deterioration. He found that mean blood glucose values in subjects treated with con[-]traceptive steroids were higher than before treatment. Marshall and Martin (15) in thei[r] studies in twenty one subjects treated with oral contraceptives for twelve months found onl[y] two patients with transient abnormalities in the first month. This did not recur in subsequen[t] months.

Pregnancy, Glucocorticoids and the Pill

It is reasonable to associate changes in glucose tolerance with pseudopregnancy pro[-]duced by the drug. Some investigators in fact reported incidence of 10 to 81% of abnorma[l] glucose tolerance in pregnancy, of which 32-66% are said to develop diabetes in 1-[7] years. Beck et al (2) studied the influence of pregnancy, gluco-corticoids and oral contracep[-]tives on oral glucose tolerance and insulin response in normal women during gestation an[d] compared these with those who had subclinical diabetes during gestation period. The ora[l] contraceptives were administered for periods extending from two weeks to two and hal[f] months, post partum. Their study indicated that oral contraceptives unmask subclinica[l] diabetes less readily than pregnancy or glucocorticoids. Further, they showed that glucocorti[-]coids inhibit insulin release in response to glucose while oral contraceptives seem to enhanc[e] insulin secretion following hyperglycaemia.

Kalkhoff (14) reported that prednisolone had a basic suppressive effect on plasma insulin in response to glucose load and this effect was potentiated by contraceptive agents i[n] normal individuals resulting in a diabetic glucose tolerance curve. The impaired toleranc[e] appeared to revert to normal when contraceptive agents were discontinued. Pi-sunyer an[d] Oster (20) have shown that the effect of oral contraceptive on glucose tolerance depends on th[e] dose employed. The improvement in glucose tolerance after small doses of oral contracep[-]tives noted by some workers with the concomitant administration of corticosteroids could b[e] due to such small doses of contraceptive agents stimulating enough insulin secretion to counte[r] the effect of glucocorticoids. That oestrogens potentiate the diabetogenic effect of adrena[l] corticoids is shown by enhanced glycosuric effect of hydrocortisone in the presence of oestrogen[s]

(17). However, subjects receiving oral contraceptives do not show any change in 17-ketosteroids and their excretion in urine. On the other hand, it is known that oestrogen increases the plasma alpha globulin "transcortin" (26) which binds hydrocortisone firmly (31) and renders it biologically inactive. This mechanism may account for blunting of the hydrocortisone effect on glucose tolerance after oral contraceptives as seen in some studies.

Differential Actions of Pill Components

Since contraceptive pill contains both the oestrogenic and progestogenic components it is reasonable to associate the changes in glucose tolerance to either of the two. Paola et al (21) observed a high incidence of abnormal prednisolone primed glucose tolerance tests in women who received mestranol. Mestranol produced these effects in women both in the reproductive state as well as in climacteric. Similar effects were not noted after the administration of ethinyl oestradiol. Wain et al (32) reported decrease in glucose tolerance in rheumatoid arthritis patients treated with large doses of Enovid. Some workers suggested that oestrogen in this combination may stimulate pituitary ACTH secretion as they do in rats (5).

In experimental diabetes in rats oestrogens have variable effects depending upon the mode of administration, sex, species of animals, duration of treatment and diet etc. (24). In subtotal pancreatectomised rats oestrogen produced an early increase and later reduction in incidence of diabetic state. In force fed normals and in alloxan diabetic rats, oestrogens temporarily increase glycosuria and hyperglycaemia. In all these experiments progesterone in moderate doses was found inactive. Oestradiol benzoate, diethyl stilbesterol and large doses of norethynodrel (5 mg for 5 days) increase fasting blood sugar levels in intact rats. In rats oestrogen seems to cause hyperglycaemic effect during early administration, but amelioration of hyperglycaemia occurs if the therapy is continued.

Benjamin and Carsper (3) studied carbohydrate metabolism in two endometrial diseases where carbohydrate metabolism was disturbed and reported an improvement in glucose tolerance after the intramuscular injection of 250 mg of 17-hydroxy progesterone, a long acting progestational compound. He also observed a depression of plasma inorganic phosphate following progesterone suggesting that this compound may act by increasing peripheral utilisation of glucose or by increasing the function of islets of pancreas. It has been shown that administration of porgesterone to rats and ferrets causes an increase in liver glycogen (8). Some workers have observed diabetogenic effect or an aggravation of experimental diabetes after progesterone treatment. In these studies however, the investigators have used very large doses of progesterone (12).

Spellacy et al (28) reported that serum growth hormone levels increase significantly after oral contraceptive treatment in normal subjects. They postulated that oral contraceptives because of their high oestrogen content cause an elevation of circulating growth hormone which produces the effect. The elevated growth hormone levels after oral contraceptive treatment may lead to an elevation of plasma insulin. Oestrogen even in small amount is sufficient to

increase the plasma protein binding thyroxin (11) and as little as 0.01 *mg* of oestrogen a day raises PBI levels in women for one to eleven months. Moreover, it has been shown that nor-ethynodrel is converted *in vivo* to a substance having oestrogenic activity. Thus oestradiol may increase the plasma protein binding of insulin as it does that of thyroxin (11) and of corticoids rendering it inactive. It is also possible that mestranol may increase the plasma insulin antagonist like synalbumin or non-esterified fatty acids (1).

Resistance to Insulin Action

Pregnancy is marked by insulin resistance (23), high serum insulinase activity and destruction of insulin by placenta (7). Non-diabetic pregnant women appear to be in a state of mild hyper insulinism as predicted by long term experiments in rats. In support of this theory are the decreased blood glucose values, increased insulin level and pancreatic hyperplasia reported in pregnancy by Spellacy and Goetz (29).

One theory proposes that there is an increased level of insulin antagonist circulating during pregnancy which could produce these effects. The insulin antagonist could be a growth hormone or a placental growth hormone or a prolactin like protein. Pregnancy has also been compared to a state of starvation because glucose is drained off from maternal circulation through placenta to the foetus and insulin is degraded by the placenta. The placenta is known to synthesise oestrogen and progesterone. Recently, Joshimovich and Maclaren (13) have shown that placenta also produces a growth hormone like protein which has growth promoting activity. One action of this growth hormone like protein could be to split triglycerides and thus elevate the levels of circulating free fatty acids. The free fatty acids can block Kreb's cycle so that there is a relative resistance to insulin action. The oestrogen and progesterone from placenta can elevate the circulating insulin levels. Thus many of the carbohydrate alterations of pregnancy may be attributed to the placental growth hormone production. It is worthwhile to note here that insulin levels are increased during pregnancy. This is similar to what has been reported following treatment with oestrogen and progesterone in normal woman.

Our Investigations

It is thus evident that the exact mode of action of oral contraceptives on carbohydrate metabolism remains an enigma. In our studies in experimental female rabbits, we have been able to produce an impairment in glucose tolerance by the oral administration of oestrogen and progesterone combination (Table 1). It appears to us that oestrogen rather than progesterone plays a major role in causing alterations in carbohydrate metabolism. We have noted that a continued oral administration of 1 *ug/kg* of ethinyl oestradiol for six months produces a definite evidence of impaired glucose tolerance (Table I). The fasting blood sugar in animals receiving oestrogen continues to be high. Further, intravenous glucose tolerance is impaired indicating that the impaired tolerance is not due to impaired absorption

of glucose.   Intravenous tolbutamide test in these animals is also impaired. In control animals intravenous tolbutamide (50 *mg/kg*) causes an immediate and prolonged hypoglycaemia.   In animals receiving oestrogen, the hypoglycaemic response to tolbutamide is impaired both in severity and duration (Fig. 1).   There is also an increased level of free fatty acids in circulation (Table 2).   Our results therefore indicate that one of the ways oestrogen may produce its action is by impairing a release of insulin from beta cells of pancreas and this in turn may set a chain of biochemical reactions such as decreased glucose tolerance and increased lipolysis. All these may lead to a diabetic state.

TABLE I: Blood glucose concentration in fasting state and after 0.75 g/kg iv glucose administration initially and after six months of contraceptive treatment.

	Blood glucose (mg%)					
	Control group		Group I		Group II	
	Initial	*Final*	*Initial*	*Final*	*Initial*	*Final*
Fasting	66 ± 7.1	73 ± 11	55 ± 3.7	117 ± 14.7	62 ± 7.2	145 ± 21.4
½ hr	250 ± 20.5	266 ± 24.7	223 ± 26.5	335 ± 47.9	302 ± 12.0	429 ± 4.0
1 hr	167 ± 20.8	197 ± 17.9	157 ± 23.7	237 ± 51.3	219 ± 30.2	387 ± 13.8
1½ hr	130 ± 18.3	135 ± 21.3	99 ± 9.6	197 ± 35.8	120 ± 2.8	259 ± 17.0
2 hr	92 ± 9.6	93 ± 11.8	81 ± 4.6	161 ± 28.8	85 ± 2.8	193 ± 15.9
2½ hr	76 ± 4.2	75 ± 10.5	54 ± 2.0	149 ± 22.2	73 ± 3.5	143 ± 20.8

Control group: 0.1 ml/kg olive oil oral.
Group I :   1 μg/kg ethinyl oestradiol and magesterol acetate 80 μg/kg orally in 0.1 ml of olive oil.
Group II :   Ethinyl oestradiol 1 μg/kg orally in 0.1 ml. of olive oil.

TABLE II.   Effect of ethinyl oestradiol (1 μg/kg orally) on free fatty acid levels.

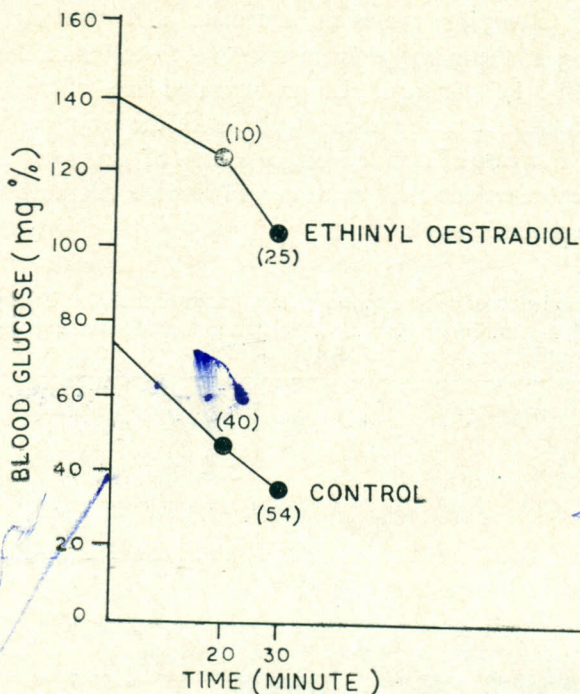|	Free fatty acid level (μ/mol/ml)	
	Control group	*Ethinyl oestradiol group.*
Initial	0.52 ± 0.028	0.6 ± 0.084
Final	0.73 ± 0.074	1.57 ± 0.106

Fig. 1.　Effect of Tolbutamide (50 mg/kg iv) in control and oestrogen treated rabbits.
Figures in parenthesis indicate the % fall in blood glucose over the initial.

Further work is necessary to elucidate the exact mechanism of carbohydrate intole-
rance in women on prolonged treatment with oral contraceptives, particularly because of
the evidence that the oral contraceptive pill can precipitate a diabetic state in women having
family history of diabetes.

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