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EFFECTS OF ORAL CONTRACEPTIVE AGENTS ON CARBOHYDRATE METABOLISM

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SUMMARY

Most investigators agree that conventional oral contraceptive agents promote contra-insulin effects in the majority of normal and diabetic subjects. The physiologic significance of these changes is not known, because the majority of women manifesting this stress will revert to their original metabolic profiles when treatment is discontinued.

Prospective studies do not support the view that oral contraceptives induce overt diabetes in truly nondiabetic subjects. There does appear to be a continuum of sensitivity to these steroids to an extent that they are often contra-indicated in most diabetic patients, particularly those who are not receiving exogenous insulin.

It is difficult to define the role of progestins in the development of changes in carbohydrate metabolism until their *in vivo* metabolism and interactions with estrogens are clarified.

It is tempting to speculate the sex steroids modify glucose metabolism in either an antagonistic or beneficial way depending on the balance between endogenous glucocorticoid-like and insulin-like effects and the preexisting status of endocrine pancreatic reserve of a specific individual.

INTRODUCTION

This review attempts to update previous appraisals and opinions [1–5] regarding the influence of conventional oral contraceptives on carbohydrate metabolism. It redirects attention first to the relative expression of diabetogenic stress among normal, subclinical and overtly diabetic subjects exposed to these hormones. Subsequently, the role of estrogen and progestin components of the oral contraceptive in the development of this stress is examined. Finally, speculation is offered regarding possible etiologies and significance of altered carbohydrate metabolism in individuals who are prescribed anti-fertility steroids.

Prospective studies of patients

With normal carbohydrate tolerance. Table 1 summarizes 22 studies of normal women whose glucose tolerance was assessed before and 1–48 months after receiving combined or sequential oral contraceptive agents. Approximately one-third of the patients were challenged with oral glucose; in the remainder, the standard intravenous method was employed.

The incidence of conversion to a diabetic test during administration of the pill ranged from 0 to 12% [2, 6–24]. Fifteen of the 22 investigations reported no incidence of the disease. The variations in reported incidence could not be attributed to differences in specific regimens or to duration of treatment. Therefore, one is forced to conclude that discrepancies in reports of carbohydrate intolerance reflect basic differences in patient selection for the various longitudinal studies.

A normal glucose tolerance test cannot be equated with nondiabetes. As everyone knows, the subclinical diabetic subject may be indistinguishable from nondiabetic individuals under ordinary circumstances. Nevertheless, deterioration into a recognizable diabetic state during periods of metabolic stress will occur such as that observed during pregnancy, following gluco-corticoid administration, or as we shall see later, the initiation of an oral contraceptive regimen.

If this supposition is correct, then the over-all incidence of diabetes (4%) in this population of 867 women most likely indicates the percentage of subclinical diabetic women who were inadvertently included in seven of the 22 studies and who converted to overt diabetes while on the "pill".

Evidence for diabetogenic stress among users of oral contraceptive agents

There are several lines of evidence to indicate that a continuum of sensitivity to sex steroids exists among all individuals receiving oral contraceptive agents. The magnitude of deterioration of glucose tolerance appears to parallel the pre-existing state of pancreatic beta cell function.

Normal women. Although nondiabetic women usually demonstrate little change in carbohydrate metabolism while on the "pill", there are several documentations of increased plasma insulin responses that significantly exceed values observed before treatment. Figure 1, taken from the work of Yen and Vela[8], illustrates this point. Twenty-three healthy

Table 1. Prospective studies of normal women: Oral and IV GTT

Test	Number of Studies	Number of Subjects	Duration of Contraception Months	Number Diabetic*
A. Oral (2,6-11)	7	264	1-48	17 (6.4%)
B. IV (8,9, 12-24)	15	603	1-36	17 (2.8%)
Totals	22	867	1-48	34 (3.9%)

* Fifteen of 22 studies reported no incidence of diabetes.

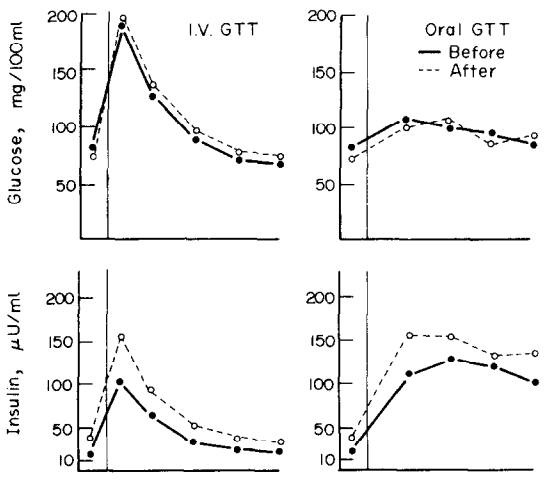

Fig. 1. Plasma glucose and insulin responses during intravenous (left panels) and oral (right panels) glucose tolerance tests. Values represent means of 23 healthy women before and after 3 months of an oral contraceptive containing ethinylestradiol plus dimethisterone or ethynodiol. From Yen and Vela[8]. Courtesy of the authors and Journal of Clinical Endocrinology and Metabolism.

women demonstrated basal and post-challenge hyperinsulinemia during both oral and intravenous glucose challenges after 3 months of conventional oral contraceptive regimens. Glucose curves, however, are essentially unchanged. This suggests that contrainsulin forces do evolve during this kind of sex steroid exposure, even in normal individuals, that necessitates compensatory increases of pancreatic insulin secretion to maintain normal glucose homeostasis.

Additional evidence suggesting the presence of stressful effects of the "pill" in normal women emerges from studies of steroid glucose tolerance tests. Table 2 summarizes the results of four different investigations in which cortisone, prednisolone or prednisone were administered to 151 women on common antifertility regimens 8-1/2 and 2 h before oral glucose tolerance testing [25–28].

It is of interest that 54% of the total group exhibited a diabetic response while on the "pill". This is 10–20 fold above that expected in a general population. Our own studies indicated that although glucose and insulin curves were normal during standard testing, diabetic glucose responses after prednisolone provocation were associated with distinctly subnormal plasma insulin increments during the first hour of the procedure [27]. In this regard, the pattern resembled

Table 2. Steroid glucose tolerance in normal women on oral contraceptives

	First Author	Number of Subjects	Contraceptive	Duration of Contraception Months	Number Diabetic
1.	Gershberg (25)	13	M + Norethynodrel+	12-60	12
2.	Terpstra (26)	16	M + Ethylestenol	3	8
3.	Kalkhoff (27)	10	M + Norethindrone	6-17	10
4.	DiPaola (28)	60	M alone or with different progestins	1-9	51
5.	DiPaola (28)	25	Norethisterone only	3-7	0
6.	DiPaola (28)	27	EE + Norethisterone	?	0
	Totals	151 patients		1-60 months	81 (54%)

*Studies 1 and 2 employed cortisone; study 3, prednisolone and studies 4-6 used prednisone.

+M: Mestranol; EE: Ethinyl Estradiol.

what is typical for age and weight-matched subclinical diabetic subjects not on oral contraceptive agents (Fig. 2). Following discontinuation of the contraceptive treatment, the steroid glucose tolerance reverted to a normal profile which could be related to a more brisk plasma insulin response (Fig. 3). These results suggested that an acquired form of subclinical diabetes exists in normal women on conventional contraceptive steroids which is reversible after the agents are discontinued.

Subclinical diabetes. The evidence for contra-insulin effects of the pill in prospective studies of subclinical diabetic patients is even more striking. Table 3 illustrates the results of four studies of women with pregnancy-onset diabetes mellitus who subsequently returned to normal glucose tolerance post-partum. The four groups of investigators then placed their subjects on different combinations of mestranol and progestins and followed their metabolic status. Fourteen out of 32 women (44%) developed overt diabetes within a relatively short period of time [29–32]. When plasma insulin responses were measured [29, 32], deterioration into a diabetic state was attended by endogenous insulin deficiency. The condition was not always reversible when the contraceptive treatment was discontinued.

The rather dramatic effects of the "pill" on a gestational (subclinical) diabetic subject is graphically illustrated in Fig. 4, data extracted from published reports of Lunell and Persson[31]. These findings also resurrect earlier statements regarding the likelihood that many women with normal control glucose tolerance tests who become diabetic on the "pill" are actually this kind of individual with an elusive, subclinical form of diabetes.

Overt diabetes mellitus. As indicated in Table 4, the majority of patients with established, non-insulin requiring diabetes mellitus show further worsening of carbohydrate tolerance after exposure to oral contraceptives [9, 25, 33–36]. In some studies, this was partially improved by concomitant administration of oral sulfonylureas [33, 34]. Gold and co-workers [34] also showed that during periods of deterioration induced by the "pill", plasma insulin responses were somewhat lower than during control testing (Fig. 5).

Nevertheless, it should be pointed out that Gershberg has demonstrated actual improvement in glucose tolerance in maturity-onset diabetics on oral contraceptive agents in a preliminary report in abstract form [58]. Moreover, Moses and Goldzieher, in their investigations of this kind of diabetic woman, have reported a definite lowering of 2-h post-prandial plasma glucose concentrations in a small group administered a combination of mestranol and chlormadinone [41]. This suggests that under certain circumstances, standard oral contraceptives may exert some beneficial effects on carbohydrate metabolism in some as yet undefined manner. More detailed studies of this phenomenon are needed, however, to document this departure from the usual trends reported to date.

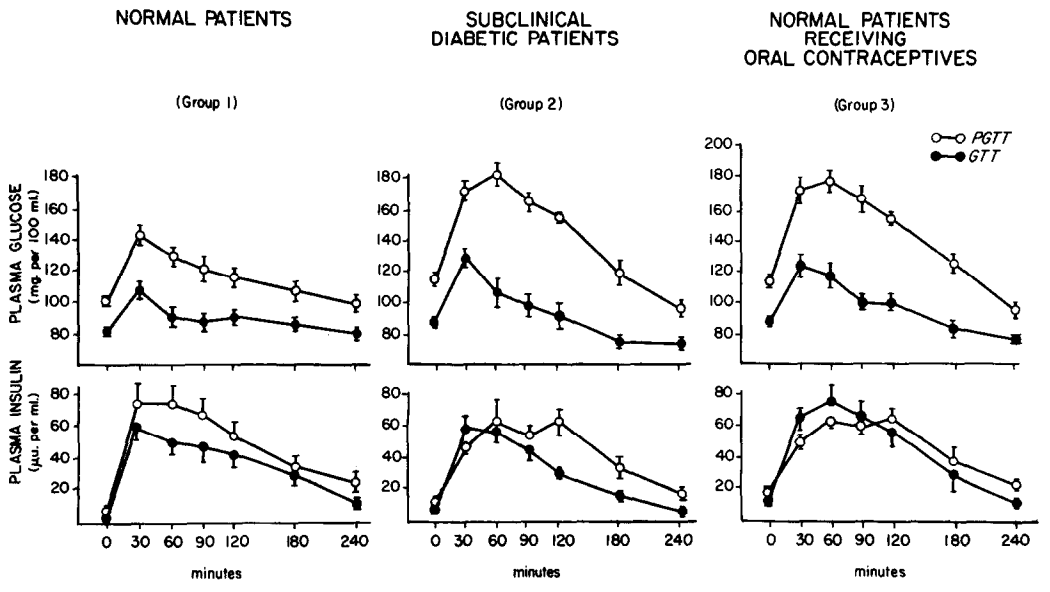

Fig. 2. Plasma glucose and insulin responses during 100g oral glucose tolerance tests (closed circles) and prednisolone glucose tolerance tests (open circles) in 10 normal women and 10 subclinical diabetic women not on oral contraceptive agents and in 10 normal women on a conventional birth control pill for 6–17 months. Values are mean ± S.E.M. From Kalkhoff, Kim and Stoddard[27]. Courtesy of the authors and Plenum Press.

Insulin-requiring diabetes mellitus. There are also a small number of studies on the effects of various oral contraceptives on diabetic women who require parenteral insulin for control. The results vary considerably. Reports of extreme lability of control are reported by some; others find no striking adverse outcome with the use of contraceptive agents and only minor readjustments of insulin dosages were required [37–40]. In no instance was improvement of the diabetic state noted. It is concluded that parenteral insulin may negate potential diabetogenic stresses of the pill in most juvenile types of diabetes, but, again, additional studies are indicated to explain why certain patients of this type do very poorly when given contraceptive steroids.

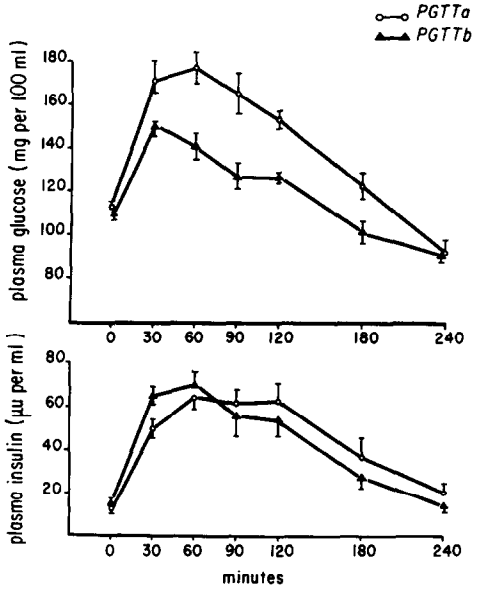

Fig. 3. Plasma glucose and insulin responses in 10 normal women during prednisolone glucose tolerance tests before (open circles) and 4–8 weeks after (closed circles) discontinuation of an oral contraceptive regimen. From Kalkhoff, Kim and Stoddard[27]. Courtesy of the authors and Plenum Press.

Relative role of estrogens and progestins in the induction of diabetogenic stress

The estrogenic components of oral contraceptive agents are usually derivatives of estradiol in the form of mestranol or ethinyl estradiol. Progestins fall into two broad categories: those related to 17-α-hydroxyprogesterone (medroxyprogesterone, chlormadinone and megestrol) and those resembling nortestosterone (norethindrone, norethynodrel, norethisterone, etc.)

In recent years attempts have been made to define the relative effects of these steroids on carbohydrate metabolism when given as single regimens. Unfortunately, these studies to date have not clearly resolved the question because of variability of results reported from one center to the next.

Oral estrogens. Eleven investigations were reviewed [22, 25, 42–47] involving 227 women who received one of four oral estrogens for periods ranging from 10 days to 36 months (Table 5). Although the great majority were unaffected by this treatment, approxi-

Table 3. Prospective studies: Subclinical diabetes*

	First Author	Number of Subjects	Regimen	Duration Months	Number Diabetic
1.	Beck (29)	12	M + Ethynodiol	1/2	2
2.	Szabo (30)	5	M + Norethindrone	4–6	5
3.	Lunnel (31)	5	M + Norethisterone	2–3	5
4.	Beck (32)	10	M + Chlormadinone	2	2
	Totals	32		1/2–6	14 (44%)

* Subclinical diabetes: diabetic glucose tolerance during pregnancy; normal tolerance post-partum.

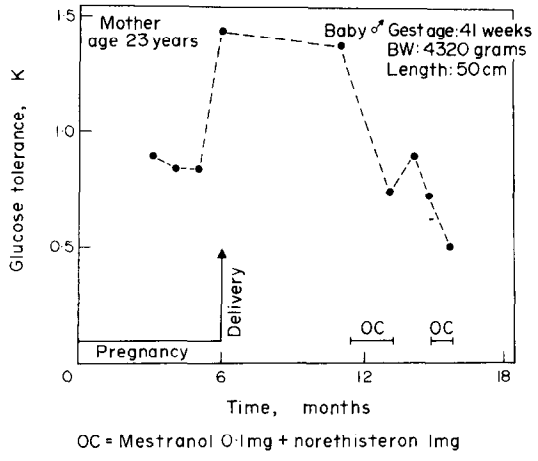

Fig. 4. Alterations of intravenous glucose tolerance during pregnancy and postpartum and during various periods of oral contraceptive administration in a gestational (subclinical) diabetic woman. From Lunnel and Persson[31]. Courtesy of the authors and Plenum Press.

mately 1/3 had some deterioration of glucose tolerance. Premarin, a form of conjugated natural estrogens, and the synthetic compound, diethystilbesterol were somewhat more adverse. The relative incidence of worsening of carbohydrate tolerance with mestranol or ethinylestradiol, the usual ingredients of contraceptive agents, was about the same and approximated 20%.

These findings have led several investigators to conclude that the estrogenic steroids in contraceptive agents are primarily responsible for the diabetogenic stress of the "pill".

Parenteral, natural estrogens. Although studies of natural sex steroid action on carbohydrate metabolism do not have specific relevance to oral contraceptive agents, they are included in this review for two reasons. First, they demonstrate a rather striking contrast to what has been reported to exist with the use of oral synthetic or semi-synthetic steroids. Second, it emphasizes the point that all estrogens do not necessarily have the same metabolic effects.

Thus, in eleven different investigations of 117 nondiabetic and diabetic subjects (Table 6), the majority (67%) improved carbohydrate tolerance and only a very small percentage of individuals (3%) worsened [48–57]. It is also of interest that many diabetic patients who improved were insulin-requiring. Parenteral estrogen treatment ranged from 1 day to 5 months and estradiol or estriol were the principal hormones administered.

Table 4. Prospective studies of maternity-onset diabetes

First Author	Number of Subjects	Regimen	Duration Months	Number Worsened	Number Improved
Goldman (33)	12	M + Norethynodrel	3	12	0
Gold (34)	10	M + Ethynodiol	1	10	0
Reder (35)	1	M + Norethynodrel	1/2	1	0
Lebherz (36)	1	M + Norethynodrel	?	1	0
Wynn (9)	7	Different regimens	?	1	0
Gershberg (25)	2	M + Ethynodiol	3-6	0	1
	33		1/2-6	24 (73%)	1

The results of these studies corroborate the original premises advanced by Houssay and co-workers [59] whose work demonstrated an antidiabetogenic effect of estradiol in diabetic rats that could be related to pancreatic islet hypertrophy. Similar findings have been reported in a variety of animal species [60–62]. In our own studies, beneficial effects of this steroid on carbohydrate metabolism in the rat were related to induction of hyperinsulinemia and augmented insulin secretion by the isolated pancreatic islet [61].

Additional investigations also revealed an inhibitory effect of natural estrogens on hepatic gluconeogenesis while accumulation of liver glycogen was concomitantly increased [75]. Others have shown that estrogens increase the sensitivity of adipose tissue and skeletal muscle to insulin action [76, 77]. It appears that when natural estrogens improve carbohydrate metabolism, they do so by reducing hepatic glucose production and increasing peripheral glucose utilization by insulin-sensitive tissues. It remains to be determined whether they have direct, betacytotrophic effects on the pancreatic islet as well.

At this point in time it is not known why differential effects of natural estrogens and oral estrogens exist with respect to carbohydrate metabolism in human subjects.

Parenteral and oral progestins. Other investigators support the premise that the progestin component of oral contraceptive agents is the primary modulator of glucose homeostasis among users of the "pill". There is some evidence to support this view [5].

Spellacy and his co-workers observed that a higher incidence of deterioration of glucose tolerance occurred in women given mestranol and ethynodiol than in women who received mestranol together with chlormadinone [10, 11]. Recall that ethynodiol is a nortestosterone derivative and chlormadinone, a relative of 17-alpha-hydroxyprogesterone. From these observations and other isolated studies it has been suggested that contraceptive preparations containing nortestosterone derivatives are more diabetogenic than those containing progesterone-like compounds [5].

Table 7 summarizes the longitudinal effects of various progestins on glucose tolerance as reported by a number of investigators [15, 32–33, 63–74]. Most of the changes under headings "worsened" or "improved" were relatively minor ones with the exception of depot medroxyprogesterone acetate. Parenteral administration of this steroid was associated with significant deterioration in a relatively large percentage of patients.

But when one examines the data comparing the relative effects of progestins of the nortestosterone type with those related to 17-α-hydroxyprogesterone, the frequency of deterioration on a percentage basis is approximately the same and the degree of worsening was comparatively minor.

One next can examine the incidence of overt dia-

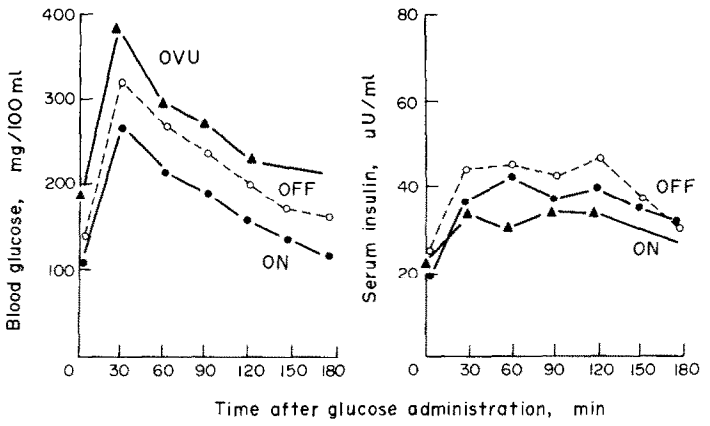

Fig. 5. Plasma glucose and insulin responses during intravenous glucose tolerance tests in ten diabetic men before (dotted lines) and after (solid triangles) 4 weeks of Ovulen treatment. "Off" and "On" refer to administration of a sulfonylurea with Ovulen. From Gold and co-workers [34]. Courtesy of the authors and Plenum Press.

betes in prospective studies of premenopausal women with normal control glucose tolerance tests. Table 8 reveals that oral estrogen administration is associated with a slightly greater incidence than that found with oral progestin treatment. There were no striking differences between the two types of progestins, and the over-all incidence of abnormal tests was not substantially different from what one might anticipate in a control population.

Phillips and Duffy recently compared plasma glucose levels 1 h after a 75 g oral glucose load among 1772 women or various oral contraceptive programs [78]. They could find no significant differences between various regimens. The type of estrogen or progestin, duration of exposure and combined or sequential treatments seemed to have little bearing on the outcome of the procedure. What they did find was a significant difference between the one hour glucose concentrations of this group and 1536 women who never used the "pill". The age-adjusted mean of the pill-users average 11 mg% higher than non-users.

Since some clinical researchers can reproduce the effects of oral contraceptive agents on glucose tolerance with oral estrogens alone [22, 24, 42–47], it seems reasonable to conclude that the estrogenic component is the primary modifier of carbohydrate tolerance; that progestins may interact with estrogens to an extent that has not been well defined.

Possible etiologies of diabetogenic stress in women receiving oral contraceptive agents

Growth hormone. Estrogens are known to augment plasma growth hormone concentrations [79] and the latter has been implicated in the development of contrainsulin effects in women receiving estrogen-containing birth control pills [8]. After more detailed studies of this relationship were done, however, there is little evidence to indicate a true cause and effect.

For example, estrogens may improve, worsen or have little effect on carbohydrate tolerance in the presence of hyperinsulinemia and elevated plasma growth hormone concentrations (Tables 5 and 6). Estrogens may alter carbohydrate tolerance in the absence of an intact pituitary in animals and man [59, 80]. These steroids may also improve carbohydrate tolerance in acromegalic subjects without affecting plasma somatotropin levels [81].

Progestins also alter glucose homeostasis in dosages considerably above that found in the pill in a way that also fails to correlate with plasma growth hormone. Thus, parenteral progesterone induces basal and postglucose challenge hyperinsulinemia without alterations of plasma glucose curves but with significant suppression of plasma growth hormone [82]. Depot medroxyprogesterone may worsen glucose tolerance despite suppression of plasma growth hormone [66, 67].

Table 5. Effects of oral estrogens on glucose tolerance*

	Estrogen	Number of Studies	Number of Subjects	Worsened	Improved	Unchanged
A.	Premarin^{R} (42-44)	3	80	28	6	44
B.	DES^{+} (43,45)	2	30	24	3	3
C.	EE^{+} (22,44)	2	30	6	0	24
D.	M^{+} (25,44-47)	4	87	18	7	64
	Totals	11	227	76 (33%)	16 (7%)	135 (59%)

* Duration of treatment ranged from 10 days to 36 months.

\+ DES: Diethystilbesterol; EE: Ethinyl Estradiol; M: Mestranol

Table 6. Effects of parenteral, natural estrogens on carbohydrate metabolism

Condition	Number of Studies	Number of Subjects	Worsened	Improved	Unchanged
A. Nondiabetic (48–50)	3	34	4	18	12
B. Diabetic (48, 51–57)	8	83	0	60	23
Totals	11	117	4 (3%)	78 (67%)	35 (30%)

* Duration of estrogen treatment: 1 day to 5 months.

Table 7. Effects of progestins on glucose tolerance

Progestin	Number of Studies	Number of Subjects	Worsened	Improved	Unchanged
1. Progesterone (63,64)	2	39	18	13	8
2. 17-alpha OH Progesterone (65)	1	18	3	10	5
3. Depot MPA (66,67)*	2	41	30	0	11
4. Oral Progesterone Derivatives (15,32,68, 69)	4	69	14	12	43
5. Oral Nortestosterone Derivatives (33,68,70–74)	7	285	56	16	213
Totals	16	452	121 (27%)	51 (11%)	280 (62%)

* MPA: Medroxyprogesterone acetate.

\+ Duration of treatment; 5 days – 12 months.

It is concluded that although estrogens and certain progestins do alter plasma growth hormone in opposite directions, these actions do not predict what eventually happens to glucose homeostasis or to plasma insulin.

Adrenal gluco-corticoids. Classic experiments of Ingle suggested that diabetes is aggravated in both adrenalectomized and intact rats given diethylstilbesterol but that the full diabetogenic effect of the estrogen requires the presence of the adrenal cortex [83]. Synergism between estrogens and gluco-corticoids in this regard has been emphasized by other researchers [84]. The nature of this interplay may be multifaceted, since estrogens have been shown to retard plasma disappearance and hepatic degradation of cortisol [85, 86], and increase plasma concentrations of free cortisol [87]. In addition, elevated serum pyruvate levels, commonly found in patients receiving gluco-corticoids, are also observed in women receiving oral contraceptive agents [9].

This background of events may also explain the vulnerability of women on anti-fertility steroids to the increased frequency of abnormal carbohydrate tolerance following exogenous administration of cortisone and related compounds [25–28].

Table 8. Oral sex steroids: Incidence of diabetes*

Steroid	Number of Subjects	Number Diabetic	Percent Diabetic
1. Estrogens (22,43–45)	94	4	4%
2. Progesterone Derivatives (15, 32, 68,69)	69	1	1%
3. Nortestosterone+ Derivatives (68, 70–74)	261	2	< 1%

* All subjects are premenopausal women with normal control glucose tolerance tests.

Glucagon. Subnormal plasma glucagon responses during intravenous arginine infusions have been reported in normal women after short term administration of oral contraceptive agents [88]. If relative hypoglucagonemia is a general effect of the "pill", then one cannot relate diabetogenic stress of oral contraceptives to disturbances of this hormone.

The dual role of sex steroids. From a clinical standpoint sex steroids, particularly estrogens, are capable of two contrasting, divergent effects. On the one hand they may induce hyperinsulinemia or act in concert with insulin to lower blood glucose and ameliorate carbohydrate tolerance. On the other hand, they may create a metabolic setting that is gluco-corticoid-like either through their own inherent properties or *via* synergistic action with endogenous adrenal gluco-corticoids or other insulin antagonists. The outcome of their administration may depend on the type of steroid employed (natural or synthetic), the route of administration, dosage, and the existing status of carbohydrate tolerance and endocrine pancreatic reserve.

The liver is the major site for translating the hypoglycemic actions of insulin. Similarly, this organ is also responsive to the hyperglycemic effects of gluco-corticoids. Since metabolism, transformation and degradation of most steroids also reside in hepatic tissue, it is likely that the effects of sex steroids on carbo-

hydrate metabolism, either directly or indirectly, involve metabolic alterations at this site.

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