on initial concentrations ($b = -0.87$) is highly significant ($t = 3.2$; D.F. = 2; $P < 0.01$).

Of the 12 patients studied prospectively six had initial serum phenytoin concentrations below 15 $\mu\text{g./ml.}$; none of these had symptoms or signs suggestive of phenytoin toxicity. All but one of the remainder had some gum hypertrophy and this was of moderate degree in the patient with the highest initial value, 51 $\mu\text{g./ml.}$ Nystagmus was induced in one patient who had a serum concentration of 40 $\mu\text{g./ml.}$ Three others were reported to show slight apathy.

Reduction in frequency of fits was not related to the increase in the mean phenytoin concentration within this group, but the relatively short period of study reduced the sensitivity of the test.

Discussion

Wide and unpredictable variation in the serum concentrations of phenytoin at first cast doubt on our methods of extraction and estimation of the drug. There was, however, no apparent source of important error; duplicate measurements under blind conditions gave reproducible results, standards in a variety of sera gave consistent readings, the absorption spectra of standards and samples were similar, and no extract from the pooled sera used for blank estimations produced an absorption band with a peak at 235 $m\mu$.

Confidence in our techniques was restored when a consistent pattern emerged between the results of the four groups of patients examined. The initial concentration of phenytoin among those studied prospectively was similar to that of the other outpatients: 17.5 and 15.7 $\mu\text{g./ml.}$ respectively (see Table). In contrast, at the end of the period of modified supervision the mean concentration among the outpatients had risen to approach that of the inpatients: 27.7 and 28.0 $\mu\text{g./ml.}$ respectively. The tendency for those patients with low initial phenytoin concentrations to show large increments during the study supports the interpretation that they were encouraged to take their drugs as prescribed. Moreover, the mean concentration attained suggests that a high degree of co-operation was achieved within the group and that the remaining disparity in serum concentrations between patients is due largely to factors other than dosage. Two inpatients and two outpatients taking only 100 mg. of phenytoin daily provided

samples containing more than 30 $\mu\text{g./ml.}$ None of the patients on the prescribed doses of 200 or 300 mg. per day attained higher concentrations, but in no instance did the concentration remain below 10 $\mu\text{g./ml.}$ It is likely that for most patients a serum concentration of 10 to 20 $\mu\text{g.}$ of phenytoin per ml. has a therapeutic effect (Buchthal *et al.*, 1960; Kutt and McDowell, 1968). Some patients can maintain this concentration on a dose of 100 mg./day, others either absorb the drug less efficiently or eliminate it more rapidly (Kutt *et al.*, 1966). None the less, failure to take treatment as prescribed is evidently an important cause of low serum concentrations in many instances.

Since in this study several modifications of outpatient supervision were introduced simultaneously, the contribution of each to improved co-operation cannot be determined. Establishment of a separate seizure clinic, more frequent appointments, provision of diary cards for recording fits, and requests for blood samples all demonstrated to the patients the increased attention given to their problem. Tablets were supplied in excess of immediate needs, so a reserve was available if the appointment was postponed. Morale appeared to improve, and premature confrontations with the patients were avoided by withholding the phenytoin values from the clinicians until the end of the study.

Little is known about the optimum use of anticonvulsant drugs because the difficulties of performing adequate controlled assessments are formidable. Clearly, no simple relation holds between prescribed dosage and serum concentration, and whenever clinical progress is unsatisfactory treatment should be modified in the light of the serum concentration rather than the oral dosage. Unreliable patients and others with a persistently low serum concentration will be detected and toxic responses resulting from inadvertent overdose should be reduced.

REFERENCES

- Buchthal, F., Svensmark, O., and Schiller, P. J. (1960). *Archives of Neurology*, **2**, 624.
- Kutt, H., Haynes, J., and McDowell, F. (1966). *Archives of Neurology*, **14**, 489.
- Kutt, H., and McDowell, F. (1968). *Journal of the American Medical Association*, **203**, 969.
- Lund, M., Jørgensen, R. S., and Kühl, V. (1964). *Epilepsia*, **5**, 51.
- Snedecor, G. W. (1956). *Statistical Methods*, 5th ed., p. 199. Ames, Iowa State University Press.
- Svensmark, O., and Kristensen, P. (1963). *Journal of Laboratory and Clinical Medicine*, **61**, 501.

Effects of Obesity, Glucocorticoid, and Oral Contraceptive Therapy on Plasma Glucose and Blood Pyruvate Levels

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Summary: The plasma glucose and blood pyruvate levels were determined after oral glucose tolerance test in six groups of women: non-obese and obese controls and in non-obese and obese women receiving glucocorticoid or oral contraceptive therapy. The mean fasting plasma glucose level was similar in all groups, but glucose tolerance was impaired in the obese controls, non-obese women on oral contraceptives or being treated with glucocorticoids, and appreciably impaired in the obese oral contraceptive and glucocorticoid groups compared with mean levels in non-obese subjects of the same groups. Obesity was associated with abnormally raised blood pyruvate levels in response to a glucose tolerance test in all

groups. Striking similarities were observed between the responses of the plasma glucose and blood pyruvate levels to glucose tolerance tests in the obese control and non-obese oral contraceptive and non-obese glucocorticoid-treated groups. It is suggested that these abnormalities result from a common mechanism—namely, glucocorticoid excess.

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Introduction

Impaired oral (Gershberg *et al.*, 1964; Wynn and Doar, 1966, 1969) and intravenous glucose tolerance (Wynn and Doar, 1966; Posner *et al.*, 1967a, 1967b) have been noted during oestrogen-progestogen therapy, but the mechanism of these changes has not been elucidated. The finding of abnormally raised blood pyruvate levels, both fasting and after glucose administration, led us to suggest that the chemical diabetes occurring during oral contraceptive therapy was "steroid diabetes," resulting from raised plasma cortisol levels induced by the oestrogen component (Wynn and Doar, 1966). More recently the finding of raised blood pyruvate levels in obese subjects (Doar *et al.*, 1968) has drawn our attention to certain metabolic similarities shared by obese subjects and those taking oral contraceptive therapy. The present study evaluates the plasma glucose and blood pyruvate levels after oral glucose tolerance test in non-obese and obese women (controls) compared with similar women receiving oestrogen-progestogen therapy or glucocorticoid drugs.

Subjects

Details of control subjects and subjects receiving oral contraceptive or glucocorticoid therapy are shown in Table I.

TABLE I.—Details of Various Groups of Subjects

Groups	No. of Subjects	Mean Age (Years)	Mean Degree of Obesity (% Ideal Body Weight)
Non-obese control	108	26	99
Obese control	51	30	150
Non-obese glucocorticoid	19	34	101
Obese glucocorticoid	6	41	137
Non-obese oral contraceptive	100	28	99
Obese oral contraceptive	29	29	139

The indications for glucocorticoid therapy were uveitis, asthma, or rheumatoid arthritis. Subjects received prednisone or prednisolone (mean daily dose 10 mg., range 4 to 25 mg.). No subject was taking any drug known to affect carbohydrate or intermediary metabolism, excepting oral contraceptives and glucocorticoid drugs. All women were advised to consume 200 g. of carbohydrate for three days before their test. Known

diabetics were excluded. Subjects were subsequently diagnosed as diabetic if they had both fasting hyperglycaemia (plasma glucose level >102 mg./100 ml.) and an abnormal oral glucose tolerance area (see below). These subjects were excluded from all three groups.

Procedures and Methods

Oral glucose tolerance tests were carried out as previously described (Wynn and Doar, 1966), a glucose load of 1 g./kg. body weight being used. Plasma glucose was measured by an automated glucose oxidase method (Cramp, 1967) and blood pyruvate by an automated enzymatic fluorimetric technique (Cramp, 1968). Plasma glucose and blood pyruvate levels in response to glucose tolerance tests were assessed as the mean levels at each time interval. Individual plasma glucose curves were also assessed as the total area between the curve and the abscissa, calculated in arbitrary units, assuming straight lines between successive points. We currently regard 800 units as the upper limit of normal in non-obese women aged 20 to 40. Standard statistical methods were used, including Student's *t* test and Snedecor's *F* test.

Results

Plasma Glucose Levels

The mean fasting plasma glucose level was similar in non-obese and obese control, glucocorticoid, and oral contraceptive groups (Tables II and III). Oral glucose tolerance, however, was relatively impaired in the obese control and non-obese glucocorticoid and oral contraceptive groups. A more pronounced deterioration of oral glucose tolerance was evident in the obese glucocorticoid and oral contraceptive groups (Tables II and III), though only the latter achieved statistical significance, probably because of the small numbers of subjects in the glucocorticoid group.

Blood Pyruvate Levels

Similar rises in the mean fasting blood pyruvate level were found in the control obese and non-obese oral contraceptive and glucocorticoid groups compared with that of the control non-obese group (Tables IV and V). Mean blood pyruvate

TABLE II.—Mean Plasma Glucose Levels after Glucose Tolerance Test in Non-Obese and Obese Control And Glucocorticoid-treated women

Time (minutes):	Mean Plasma Glucose $\pm$ S.D. (mg./100 ml.)						
	Pre	30	60	90	120	150	180
Control non-obese women	83.6 $\pm$ 8.9	132.3 $\pm$ 21.9	124.6 $\pm$ 22.8	112.2 $\pm$ 22.2	105.1 $\pm$ 20.7	90.6 $\pm$ 19.7	82.0 $\pm$ 17.3
Control obese women	84.6 $\pm$ 9.9	138.2 $\pm$ 22.9	140.9 $\pm$ 34.9	134.6 $\pm$ 34.3	127.9 $\pm$ 30.5	110.9 $\pm$ 30.3	92.8 $\pm$ 30.6
Glucocorticoid non-obese women	83.9 $\pm$ 8.5	137.5 $\pm$ 22.5	141.6 $\pm$ 20.7	131.0 $\pm$ 44.2	118.8 $\pm$ 37.1	103.1 $\pm$ 32.1	88.4 $\pm$ 23.3
Glucocorticoid obese women	84.7 $\pm$ 7.7	139.7 $\pm$ 19.7	159.8 $\pm$ 31.2	165.2 $\pm$ 42.8	149.8 $\pm$ 34.6	122.3 $\pm$ 24.5	105.7 $\pm$ 26.9
Significance of differences of means (<i>P</i> <)							
Control non-obese <i>v.</i> control obese	N.S.	N.S.	0.01	0.001	0.001	0.001	0.05
Glucocorticoid non-obese <i>v.</i> glucocorticoid obese	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Control non-obese <i>v.</i> glucocorticoid non-obese	N.S.	N.S.	0.01	0.01	0.05	0.05	N.S.
Control obese <i>v.</i> glucocorticoid obese	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE III.—Mean Plasma Glucose Levels after Glucose Tolerance Test in Non-Obese and Obese Control Women and Women Receiving Oral Contraceptive therapy

Time (minutes):	Mean Plasma Glucose $\pm$ S.D. (mg./100 ml.)						
	Pre	30	60	90	120	150	180
Control non-obese women	83.6 $\pm$ 8.9	132.3 $\pm$ 21.9	124.6 $\pm$ 22.8	112.2 $\pm$ 22.2	105.1 $\pm$ 20.7	90.6 $\pm$ 19.7	82.0 $\pm$ 17.3
Control obese women	84.6 $\pm$ 9.9	138.2 $\pm$ 22.9	140.9 $\pm$ 34.9	134.6 $\pm$ 34.3	127.9 $\pm$ 30.5	110.9 $\pm$ 30.3	92.8 $\pm$ 30.6
O.C. non-obese women	84.9 $\pm$ 5.5	136.4 $\pm$ 20.5	139.3 $\pm$ 26.6	131.8 $\pm$ 27.5	122.6 $\pm$ 25.0	107.6 $\pm$ 20.5	96.2 $\pm$ 20.3
O.C. obese women	87.7 $\pm$ 8.7	147.9 $\pm$ 21.7	159.4 $\pm$ 30.8	154.3 $\pm$ 28.8	145.3 $\pm$ 30.3	133.2 $\pm$ 28.7	118.9 $\pm$ 28.4
Significance of differences of means (<i>P</i> <)							
Control non-obese <i>v.</i> O.C. non-obese	N.S.	N.S.	0.001	0.001	0.001	0.001	0.001
Control obese <i>v.</i> O.C. obese	N.S.	N.S.	0.05	0.01	0.05	0.01	0.001
O.C. non-obese <i>v.</i> O.C. obese	N.S.	0.05	0.01	0.001	0.001	0.001	0.001

levels were also much higher in these three groups after oral glucose administration. Mean blood pyruvate levels were even higher in the obese glucocorticoid and obese oral contraceptive groups (Tables IV and V). The variances of blood

in three metabolic situations—namely, obesity, oral contraceptive therapy, and glucocorticoid administration. The combination of obesity and glucocorticoid or oral contraceptive therapy exerted an additive effect on the impairment of glucose

TABLE IV.—Mean Blood Pyruvate Levels after Glucose Tolerance Test in Non-Obese and Obese Control and Glucocorticoid-Treated Women

Time (minutes):	Mean Blood Pyruvate $\pm$ S.D. (mg./100ml.)					No. of Subjects	Mean Degree of Obesity (% I.B.W.)
	Pre	30	60	90	120		
Control non-obese women	0.55 $\pm$ 0.16	0.71 $\pm$ 0.25	0.96 $\pm$ 0.26	0.88 $\pm$ 0.21	0.76 $\pm$ 0.17	108	99
Control obese women	0.72 $\pm$ 0.30	0.99 $\pm$ 0.43	1.24 $\pm$ 0.43	1.12 $\pm$ 0.29	0.96 $\pm$ 0.25	51	150
Glucocorticoid non-obese women	0.81 $\pm$ 0.40	1.05 $\pm$ 0.44	1.28 $\pm$ 0.44	1.17 $\pm$ 0.38	0.99 $\pm$ 0.31	19	101
Glucocorticoid obese women	0.78 $\pm$ 0.20	1.08 $\pm$ 0.27	1.69 $\pm$ 0.43	1.66 $\pm$ 0.37	1.33 $\pm$ 0.29	6	137

Significance of differences of means ($P <$)

Control non-obese v. control obese	0.001	0.001	0.001	0.001	0.001	
Glucocorticoid non-obese v. glucocorticoid obese	N.S.	N.S.	N.S.	0.01	0.05	
Control non-obese v. glucocorticoid non-obese	0.001	0.001	0.001	0.001	0.001	
Control obese v. glucocorticoid obese	N.S.	N.S.	0.05	0.01	0.01	

TABLE V.—Mean Blood Pyruvate Levels After Glucose Tolerance Test in Non-Obese and Obese Control Women and Women Receiving Oral Contraceptive Therapy

Time (minutes):	Mean Blood Pyruvate $\pm$ S.D. (mg./100 ml.)					No. of Subjects	Mean Degree of Obesity (% I.B.W.)
	Pre	30	60	90	120		
Control non-obese women	0.55 $\pm$ 0.16	0.71 $\pm$ 0.25	0.96 $\pm$ 0.26	0.88 $\pm$ 0.21	0.76 $\pm$ 0.17	108	99
Control obese women	0.72 $\pm$ 0.30	0.99 $\pm$ 0.43	1.24 $\pm$ 0.40	1.12 $\pm$ 0.29	0.96 $\pm$ 0.25	51	150
O.C. non-obese women	0.71 $\pm$ 0.28	0.90 $\pm$ 0.34	1.23 $\pm$ 0.37	1.15 $\pm$ 0.33	0.94 $\pm$ 0.27	100	99
O.C. obese women	0.79 $\pm$ 0.29	1.14 $\pm$ 0.41	1.57 $\pm$ 0.50	1.43 $\pm$ 0.40	1.20 $\pm$ 0.32	29	139

Significance of differences of means ($P <$)

Control non-obese v. O.C. non-obese	0.001	0.001	0.001	0.001	0.001	
Control obese v. O.C. obese	N.S.	N.S.	0.01	0.001	0.001	
O.C. non-obese v. O.C. obese	N.S.	0.01	0.001	0.001	0.001	

pyruvate levels of the control obese and non-obese glucocorticoid and non-obese oral contraceptive groups were significantly greater than those of the non-obese control group (Tables VI and VII).

TABLE VI.—Significance of Ratios of Variances of Glucose Tolerance Test Blood Pyruvate Levels in Non-Obese and Obese Control and Glucocorticoid-Treated Women

Time (minutes)	Significance of F ($P < $)				
	Pre	30	60	90	120
Control non-obese v. glucocorticoid non-obese	0.01	0.01	0.01	0.01	0.01
Control obese v. glucocorticoid obese	N.S.	N.S.	N.S.	N.S.	N.S.
Control non-obese v. control obese	0.01	0.01	0.01	0.01	0.01

TABLE VII.—Significance of Ratios of Variances of Glucose Tolerance Test Blood Pyruvate Levels in Non-Obese and Obese Control Women and Women Receiving Oral Contraceptive Therapy

Time (minutes)	Significance of F ($P < $)				
	Pre	30	60	90	120
Control non-obese v. O.C. non-obese	0.01	0.01	0.01	0.01	0.01
Control obese v. O.C. obese	N.S.	N.S.	N.S.	0.05	N.S.

The response of the plasma glucose and blood pyruvate levels to glucose tolerance tests in the obese control and non-obese glucocorticoid and oral contraceptive groups showed striking similarities (see Figs. 1 and 2 overleaf).

The present study has shown oral glucose tolerance to be relatively impaired, in the absence of fasting hyperglycaemia,

tolerance. Obesity was also associated with raised blood pyruvate levels in control, glucocorticoid, and oral contraceptive groups of subjects. Glucose tolerance tests revealed striking similarities of plasma glucose and blood pyruvate levels in the obese control, non-obese oral contraceptive, and non-obese glucocorticoid groups of subjects. These observations are compatible with, but do not prove, the hypothesis that the abnormalities of plasma glucose and blood pyruvate levels in obesity and during oral contraceptive or glucocorticoid administration to non-obese subjects result from a common mechanism. We have suggested that the liver may be exposed to glucocorticoid excess in all three situations (Doar *et al.*, 1969).

Though the raised plasma cortisol levels during oestrogen administration are mainly due to an increase of protein-bound cortisol, thought to be biologically inactive (Matsui and Plager, 1966), recent work (Keller *et al.*, 1969) suggests that this fraction may exert biological activity in certain tissues with protein-permeable vascular beds such as the liver. Keller *et al.* (1969) found that the activity of alanine aminotransferase was increased by previous treatment with corticosterone in both rat liver and pancreas tissue. When the plasma corticosterone level was raised by oestrogen treatment, however, only the hepatic enzyme responded with increased activity. Furthermore, recent studies have indicated that the non-protein-bound plasma cortisol levels are also increased during oestrogen therapy (Burke, 1969; Sandberg *et al.*, 1969). This explanation of the effects of oral contraceptive therapy on plasma glucose and blood pyruvate levels in response to glucose tolerance tests assumes that similar changes are found during oestrogen therapy alone. There have been few studies of oestrogen or

progestogen therapy administered singly, but the available evidence indicates that the oestrogen component alone can account for the abnormalities of glucose tolerance (Javier *et al.*, 1968; Goldman *et al.*, 1968; Goldman and Ovadia, 1969) and blood pyruvate levels (Doar *et al.*, 1969) during combined

Fig. 1.—Mean O.G.T.T. plasma glucose levels. Fig. 2.—Mean O.G.T.T. venous blood pyruvate level.

oestrogen-progestogen therapy. Circulating plasma cortisol levels are usually normal in obesity, but the cortisol production rate is often increased (Schteingart and Conn, 1965). The hepatic clearance of cortisol is therefore increased and a local effect on hepatic glucose and pyruvate handling is possible.

Obesity (Perley and Kipnis, 1966a), oral contraceptive therapy (Wynn and Doar, 1969), and glucocorticoid therapy (Perley and Kipnis, 1966b) are associated with raised plasma insulin levels in response to a glucose tolerance test. Since plasma glucose levels are also increased, it appears that there is increased resistance in one or more tissues to the actions of insulin. Studies of pyruvate metabolism using a sodium L (+) lactate infusion technique have suggested that the abnormally raised blood pyruvate levels in obesity, and during glucocorticoid or oral contraceptive therapy, are caused by an increased proportion of the glucose load passing down the glycolytic pathway to pyruvate rather than an impaired rate of removal of this metabolite (Doar *et al.*, 1969; Doar and Cramp, in preparation). If the peripheral insulin resistance referred to above were to affect non-glycolytic pathways of glucose metabolism more than the glycolytic pathway, the combination of raised plasma glucose and insulin levels could result in an increased rate of formation of pyruvate from glucose in certain tissues.

The increased variance of blood pyruvate levels in response

to a glucose tolerance test in the non-obese oral contraceptive and glucocorticoid groups may reflect the heterogeneous nature of the drug therapy. The type of drug and dose and duration of therapy varied widely within each group. We have been unable to detect, however, a relation between any one of these factors and the change of blood pyruvate levels during oral contraceptive therapy (Doar *et al.*, 1969). The increased variance in the control obese group may be due to the greater range of degree of obesity of these subjects compared with that of the non-obese group, since we have previously found a significant correlation ($r=0.32$, $P<0.01$) between the fasting blood pyruvate level and the degree of obesity in non-diabetic women (Doar *et al.*, 1968).

The abnormalities of blood pyruvate levels in response to a glucose tolerance test reported here differ from those observed in maturity-onset diabetes mellitus. In a detailed study (Doar *et al.*, in preparation) we have found no influence of diabetes mellitus (either maturity-onset or insulin-requiring) on the fasting blood pyruvate level. The mean fasting blood pyruvate level, however, was higher in obese than non-obese diabetic subjects. Mean blood pyruvate levels were higher in both obese and non-obese maturity-onset diabetic subjects during the later stages of the test compared with mean blood pyruvate levels in non-diabetic subjects of similar degree of obesity.

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REFERENCES

- Burke, C. W. (1969). *British Medical Journal*, **2**, 798.
 Cramp, D. G. (1967). *Journal of Clinical Pathology*, **20**, 910.
 Cramp, D. G. (1968). *Journal of Clinical Pathology*, **21**, 171.
 Doar, J. W. H., Wynn, V., and Cramp, D. G. (1968). *Metabolism*, **17**, 690.
 Doar, J. W. H., Wynn, V., and Cramp, D. G. (1969). In *Metabolic Effects of Gonadal Hormones and Contraceptive Steroids* (edited by H. A. Salhanick, D. M. Kipnis, and R. L. Vande Wiele, p. 178). New York, Plenum Press.
 Gershberg, H., Javier, Z., and Hulse, M. (1964). *Diabetes*, **13**, 378.
 Goldman, J. A., and Ovadia, J. L. (1969). *American Journal of Obstetrics and Gynecology*, **103**, 172.
 Goldman, J. A., Ovadia, J. L., and Eckerling, B. (1968). *Israel Journal of Medical Sciences*, **4**, 878.
 Javier, Z., Gershberg, H., and Hulse, M. (1968). *Metabolism*, **17**, 443.
 Keller, N., Richardson, U. I., and Yates, F. E. (1969). *Endocrinology*, **84**, 49.
 Matsui, N., and Plager, J. E. (1966). *Endocrinology*, **78**, 1159.
 Perley, M., and Kipnis, D. M. (1966a). *Diabetes*, **15**, 867.
 Perley, M., and Kipnis, D. M. (1966b). *New England Journal of Medicine*, **274**, 1237.
 Posner, N. A., Silverstone, F. A., Pomerance, W., and Baumgold, D. (1967a). *Obstetrics and Gynecology*, **29**, 79.
 Posner, N. A., Silverstone, F. A., Pomerance, W., and Singer, N. (1967b). *Obstetrics and Gynecology*, **29**, 87.
 Sandberg, A. A., Rosenthal, H. E., and Slaunwhite, W. R., jun. (1969). In *Metabolic Effects of Gonadal Hormones and Contraceptive Steroids*, edited by H. A. Salhanick, D. M. Kipnis, and R. L. Vande Wiele, p. 367. New York, Plenum Press.
 Schteingart, D. E., and Conn, J. W. (1965). *Annals of the New York Academy of Sciences*, **131**, 388.
 Wynn, V., and Doar, J. W. H. (1966). *Lancet*, **2**, 715.
 Wynn, V., and Doar, J. W. H. (1969). In *Metabolic Effects of Gonadal Hormones and Contraceptive Steroids*, edited by H. A. Salhanick, D. M. Kipnis, and R. L. Vande Wiele, p. 219. New York, Plenum Press.

Contraception with Chlormadinone Acetate in Woman with Previous Contraceptive Jaundice

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Summary: The oral contraceptive chlormadinone acetate has been given for eight months to a woman who had developed jaundice during four pregnancies, and twice while taking a combined contraceptive pill. No side-effects or changes in liver function were observed. This is further evidence that progestogens used for contraception, and in particular those derived from hydroxyprogesterone, are less hepatotoxic than the oestrogenic components.

Introduction

About a third of the women who develop jaundice while taking a contraceptive pill have previously had itching or cholest-

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