

RES MEDICA

Journal of the Royal Medical Society



The Chocolate Coated Pill

Roger H. Smith
B.Sc.

Abstract

From a dissertation on the side effects of Oral Contraceptives, read before the Society on Friday, 2nd December, 1966

The great increase in the world birth rate that is presently taking place, and which increases the population by 165,000 people per day, has been estimated to double the total human population by the turn of the century.

The problems set by such a rise in numbers is not confined to the East or to the "underdeveloped" countries of Africa, but is calculated to increase the population of Britain by 50% in those same thirty-odd years.

Copyright Royal Medical Society. All rights reserved. The copyright is retained by the author and the Royal Medical Society, except where explicitly otherwise stated. Scans have been produced by the Digital Imaging Unit at Edinburgh University Library. Res Medica is supported by the University of Edinburgh's Journal Hosting Service: <http://journals.ed.ac.uk>

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, April 1967, 5(4): 39-44

doi: [10.2218/resmedica.v5i4.500](https://doi.org/10.2218/resmedica.v5i4.500)

THE CHOCOLATE COATED PILL

Roger H. Smith, B.Sc.

From a dissertation on the side effects of Oral Contraceptives, read before the Society on
Friday, 2nd December, 1966

The great increase in the world birth rate that is presently taking place, and which increases the population by 165,000 people per day, has been estimated to double the total human population by the turn of the century. The problems set by such a rise in numbers is not confined to the East or to the "under-developed" countries of Africa, but is calculated to increase the population of Britain by 50% in those same thirty-odd years.

Clearly, something has to be done to check this growth which far outstrips the foreseeable increase in food resources, and even more clearly the answer is birth control, in one way or another. In Britain at present the control is largely by two methods, the oral contraceptive and the intrauterine device (IUD), so that in 1965 over 500,000 women in this country were taking one or other form of pill at some time, and 400,000 took pills over a 12 month period without a break. But at the same time, the Pill has come in for much adverse criticism for its possible or actual side effects in both the lay and the scientific press, and as a result, there has grown suspicion and fear in many women and not a few doctors whose job it is to prescribe the Pill.

THE PILLS

In Britain the main drugs in use are com-

bined progestin/oestrogen preparations, taken between days five and twenty-five of the menstrual cycle. Nine such preparations are approved by the Council for the Investigation of Fertility Control (CIFC), the research branch of the FPA. This paper will consider the evidence regarding the side effects of this type of pill alone.

Another type of Pill has recently been developed and marketed, known as the Sequential Therapy type, where pure progestin is given between days 5 - 20 followed by five days of combined pills. But a certain failure rate does not allow as much confidence in these as in the combined forms, and for this reason only the combined form will be considered.

POSSIBLE SIDE EFFECTS

There are well established side effects to the Pill, such as initial nausea and vomiting in some women, but there are other effects not so well established, like liver damage, increased risk of thrombo-embolic disease, weight gain and other metabolic changes; this paper seeks to correlate the evidence available regarding these doubtful effects.

WEIGHT GAIN

It has been said that the weight gain during oral contraceptive therapy presents no problem. It was a man who said it, and not a woman,

Progestin	mg.	Oestrogen additive		Trade Name
		Mestranol mg.	Ethyinyl Oestra- diol mg.	
Lynestranol	5.0	0.15	—	Lyndiol
Megestrol	4.0	—	0.05	Volidan
Norethisterone	2.0	0.10	—	Orthonovin
Norethisterone ac	2.5	—	0.05	Norlestrin
Norethisterone ac	4.0	—	0.05	Anovlar
Norethynodrel	2.5	0.10	—	Conovid E
Norethynodrel	5.0	0.075	—	& Previson
Ethynodiol diac	1.0	0.1	—	Conovid
				Ovulen

Fig. 1. Combined Therapy Pills approved by C.I.F.C.

and it was in a medical rather than a philosophical context that it was said. When we talk about a weight gain we must consider the age group and sex of the subjects involved, and here we are dealing with women between the ages of 16 and 50, the very people to whom any weight gain seems important. So that, far from presenting no problem, weight gain could prove to be a deciding factor to any woman considering whether to take the Pill for the first time, or whether to continue taking it having once started therapy. Before we pass this off as of minor importance, we should at least examine the incidence and extent of weight gains during therapy, and investigate the cause and nature of the gain.

In a recent study, the C.I.F.C. found that treatment with Anovlar is associated with a high incidence of weight gain; of 156 patients studied, 46% put on more than 3lbs. and 22% gained more than 7 lbs. Liggins, using larger doses of Anovlar in the treatment of dysfunctional uterine bleeding, found general increases of weight of up to 9 lbs., and one case of a gain of 20 lbs., all over similar periods of time. But Wiseman has found that treatment with compounds other than Anovlar, such as Conovid or Ovulen, give equivocal results, weight gains over 3 lbs. being matched by a similar incidence of weight loss greater than 3 lbs.

While comparing their actions in a different context, Jackson found that Anovlar had a predominately progesterone-like influence on the reproductive organs but Conovid gave a more oestrogenic picture. Thus, in those women on Anovlar there was a dormant, hypoplastic endometrium, with thick, scanty cervical mucus, while women on Conovid had cornified vaginal epithelium and proliferative endometrium.

It is conceivable that weight gain in Anovlar therapy, then, is the expression of progesterone-like properties of its progestin, Norethisterone, while the progestin of Conovid, or of Ovulen, having less progesterone-like activity and more oestrogenic properties, would not be expected to stimulate a gain in weight. Such a hypothesis is supported by evidence which suggests that Progesterone itself is an anabolic agent.

Dewar has shown conclusively that the maintenance of the weight gain of pregnancy in mice is dependent upon circulating Progesterone; furthermore, Progesterone administered to male and non-pregnant female mice produced weight gain, and this gain was uninfluenced by coincident oestrogen administration. Such gains were associated with increased appetite, and were the "manifestations" of the accumulation of body fat and body water, regardless of diet. On unrestricted diets there were also increases in body protein.

During human pregnancy, the mother's weight gain is associated with rising blood Progesterone levels; not all of this weight gain is due to increased body water for there is a considerable increase in body nitrogen. The weight gain of oral contraceptive therapy would likewise seem to be anabolic, at least in part, for the fall in weight which follows the cessation of therapy in such cases is slow, spread over several weeks or months, and its rate of fall is not affected to any significant degree by the application of diuretics.

These lines of evidence suggest that progesterone-like therapy, including some oral contraceptives, can be expected to carry with it the possibility of weight gain of an anabolic nature. But a further factor may act in addition to anabolic influence, per se.; that is, increased appetite. The increased appetite might be

seen as part of the anabolic effect, but it might be preferable to think of it rather as a manifestation of the general "new lease of life" so widely reported by patients introduced to oral contraception. If this is so, then dieting may often be a necessary accompaniment of therapy.

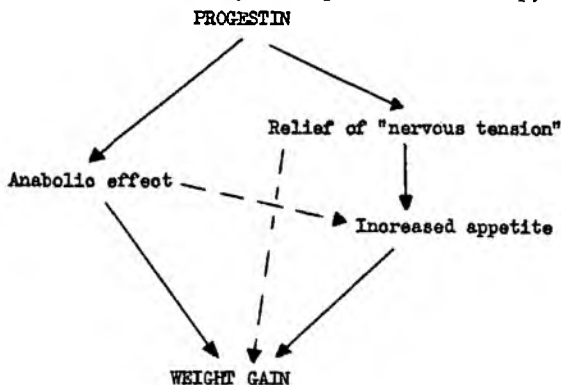


Fig. 2

The effect on appetite would also help explain why other studies, such as that by Flowers, have found weight gains with Ovulen and other products other than Anovlar; indeed, one woman out of 200 on Ovulen gained 20 lbs. in three months.

The conclusion, then, must be that weight gain can be a medical problem, and hence women or oral contraceptive therapy should be followed up; and usually the problem is a psychological one to the patient, which might call for advice. In order to give advice where it is needed we must be presented with more hard facts from large scale studies of weight and appetite in treated women, and, where gains occur, of the nature of this gain.

BLOOD COAGULABILITY

Much has been made of the assertion that synthetic steroids might increase blood coagulability. While reporting in the medical journals has stimulated a proper study of the problem, the reaction to the advertising in the newspapers has bred a fear of oral contraceptives in many women. Two lines of study have been pursued :

- (1) a large scale statistical comparison of the incidence of thrombo-embolic disease in women taking oral contraceptives and those of the same age-group not undergoing therapy.
- (2) haematological investigations in the treated and non-treated groups.

(1) Haematology

Behind the word "coagulability" there are

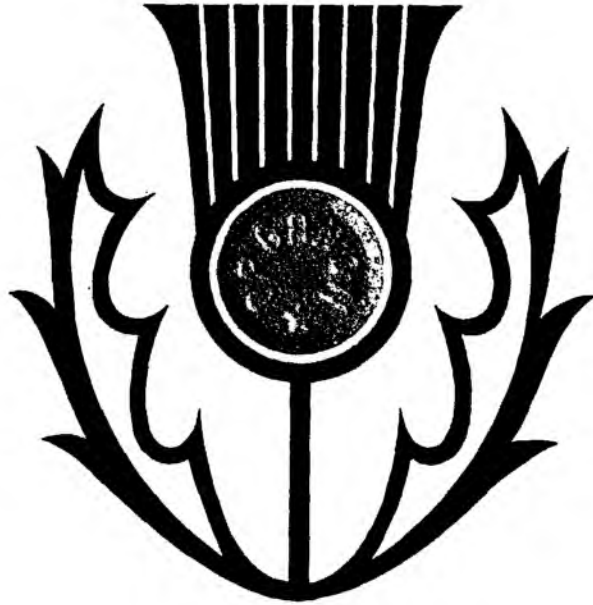
two primary processes of remarkably similar complexity, coagulation and fibrinolysis. Each comprises of a system of precursors and activators; each depends upon successive steps of activation; in each there is a number of negative systems tending to antagonise the various activation steps and products. The two processes are currently thought to be in dynamic equilibrium in the circulating blood, pivoting round the fibrin molecule: the one process forms the clot, the other destroys it. Any change in blood coagulability is the result of an upset of this normal equilibrium. In assessing the effect of an increased activity of any one part of either system, one must consider whether there is not also a change in the activity of a factor or factors in the opposing system. In any event, the interpretation of such a rise within its own system is a very difficult task.

The only factor which has consistently been shown to change is factor VII of the coagulation system; its blood concentration increases. No other coagulating factor has been demonstrated to change in any reproducible manner. Factor VII also increases in pregnancy, and is increased in patients with recent DVT ("Deep Venous Thrombosis"), but only in these latter cases has there been demonstrated a shortening of the heparin clotting time. If an increase in factor VII, per se, is contributory to greater clotting tendencies, such increases as have been shown still cannot be said to constitute satisfactory evidence for increased coagulability. There is neither any information regarding the state of the fibrinolytic system during therapy, nor of any influence that the synthetic steroids might have on the antithrombin and other systems.

Therapy	No.	Bleeding time (secs)	Clotting time (secs)
Control	26	145 ± 8.21	278.8 ± 10.7
Medication	39	116.8 ± 6.31	261.5 ± 7.02
3 - 8 months Post			
Medication	10	103.4 ± 12.4	223.9 ± 15.5

Fig. 3. Significant results (bold type) found with 10 mg Conovid Dosage (after Pincus, 1956).

The only information that can safely be accepted as evidence either way is that showing change in clotting or bleeding times. Pincus, in his classical trials using Conovid, did find shortening of bleeding and clotting times, but using 10 mg doses rather than the 5 mg used



You already know

Lyndiol 2.5 to be the oral contraceptive
with the lowest incidence of side-effects,
the most reasonable price-to-patient
and the dosage scheme most likely to
ensure patient reliability

**But did you also know
that Lyndiol 2.5 is
MADE IN SCOTLAND!**

lynestrenol 2.5 mg. mestranol 0.075 mg.

Detailed professional and patient literature gladly sent on request



Organon Laboratories Limited
Newhouse · Motherwell · Lanarkshire

in more modern therapy. No such results were found in the studies of Egeberg or of Thompson whose work is referred to above.

(2) Statistical Surveys

Agencies of the U.S. Government have carried out large scale statistical surveys, and have concluded that "there is no increase in the incidence of thrombotic disease in women taking oral contraceptives compared with the incidence in non-pregnant women of the same age group who are not treated".

There have been many isolated reports of thrombo-embolic disease in treated women, but it is important to consider that a certain incidence is in any case expected in women of this age group, whether or not they are taking the pill. It is the view of the Dunlop Committee that the incidence in treated women is indeed just that expected on this basis; but the Committee is nevertheless urging that all thrombo-embolic incidents in treated women should be reported. However, by the time statistical analysis is possible and is available, it is likely that the present form of pill will be obsolete.

HEPATOXICITY

Many drugs have been shown to be toxic to the liver, a fact that should not be surprising, for the liver is the main site of drug detoxication and excretion, and it is the first port of call for oral drugs once absorbed into the blood. Cholestatic jaundice of a non-sensitive type has been shown to develop in relation to therapy with the general group of steroids alkylated at the C-17 position, to which group belong most of the progestins presently used in oral contraceptive preparations. The general rule is that the C-17 alkylated steroids cause liver damage if given often enough and in sufficient amounts, so that the problem here is whether

the amounts of these compounds in the various pills constitute a risk of hepatotoxicity.

Many studies have been carried out attempting to determine just this one simple fact, only to find that the answer is not so simple.

There seems to be no common plan to the studies, each one having employed a different drug or combination of drugs on different groups of women in different countries and using different criteria for liver damage. But, complicated as this might seem, it is possible to draw certain conclusions on the subject, and to see certain general trends.

Scandinavian workers have been able to demonstrate quite widespread liver damage in treated women, while elsewhere the conclusion has been that there is no danger of associated hepatotoxicity during normal contraceptive therapy. In Finland, abnormally raised serum transaminase levels were found by Eisalo et al in all of seven post-menopausal women treated, and by Palva and Mustala in five. Eisalo gave one or two tabs. per day of Lyndiol; Palva used Anovlar. Eisalo was later able to reproduce his results in a number of cyclical women between the ages of 17 - 52 using Volidan as well as Lyndiol or Lynestranol.

Other isolated reports have come from Scandinavia, so that it has been suggested that the apparent high incidence of liver damage there might be connected with the fact that viral hepatitis takes an unusually virulent form in this geographical area. However, Borglin in Sweden has not been able to demonstrate hepatotoxicity in patients on Lyndiol.

In a British report on liver damage, by Aascher and Cuthbert, five post-menopausal women had been treated with Anovlar; their ages were between 62 - 80. Stoll in Australia produced

Fig. 4. Abnormal results of liver function tests
(Eisalo et al 1965)

DRUG	Total Patients	SGOT		SGPT	
		No. of Abnormals	Units (mean)	No. of Abnormals	Units (mean)
Volidan	45	0	-	2	52-73 (62.5)
Lyndiol	39	6	43-79 (58)	7	41-115 (68.2)
Lynestranol	25	1	42	1	69

liver damage in treating breast cancer with 6 tabs per day of Lyndiol, equal to 30 mg lynestranol + 0.9 mg mestranol; clearly this represents an abnormally massive dose, but it does serve to illustrate that these are potentially very dangerous drugs.

Thus there would seem to be two important factors in the aetiology of liver damage in treated women; one a possible post-menopausal predisposition to drug induced intra-hepatic cholestasis, and the other the possible predisposition due to previous liver disease. A third possibility has been suggested, that Scandinavian women, and post-menopausal women in general, share some common enzyme deficiency.

More reassuring are the results of a large scale study, by Tyler in Los Angeles, which covers eight years of observation. Tyler reports a general incidence of abnormal liver function, but in each case the changes have been of the order expected in normal pregnancy; it seems fair to conclude that these changes, due to a variety of preparation, might not be pathological but attributable rather to the pseudo-pregnant state. More specifically, he studied 6,500 cycles in 435 women on Orthonovin over a period of 3 years, during which time he found no abnormality which could cause alarm, and certainly no indication in any patient that the pill should be discontinued by reason of liver damage. Swyer and Little working in Britain have failed to demonstrate any liver malfunction in a group of 12 women treated

for a minimum period of 3 years. Similarly, workers in other parts of the world outside Scandinavia have failed to find evidence of liver damage in normal treatment.

Thus, apart from incidences in post-menopausal women, or where large doses of drugs have been used, the only reports of hepatic dysfunction have come from Scandinavia, and from Finland in particular. The pill would therefore seem to be safe as a contraceptive except for the one exception of women with a history of liver disease.

CONCLUSION

Having investigated the three problems of weight gain, thrombo-embolic disease and liver damage, it is apparent that there is little in the way of definite scientifically based conclusion to be made. While the scanty evidence available at present allows of reasonable generalisation, it also calls for more investigation. Another twenty years of study could clarify the implications of therapy, but by that time the present form of the pill will have been superseded.

Not every woman taking the pill is destined to become obese and yellow, with massive DVT; it would be unrealistic to think so. But it would be equally ill-informed to ignore the real risks. However, the risks that seem to operate are greatly outweighed by the tremendous social therapeutic advantages of oral contraceptive therapy.

REFERENCES

- Liggins, Jackson, Mears: "Recent Advances in Ovarian and Synthetic Steroids and the control of ovarian function". Sidney Symposium, 1964. ed. Shearman.
- Dewar. Q. J. Ex. Physiol., 1957, 15, 216-229.
- Dewar. Q. J. Ex. Physiol., 1964, 49, 151.
- Egeberg and Owren. B.M.J., 1963, i, 220.
- Thomson and Poller. B.M.J., 1965, i, 1586.
- Food and Drugs Administration, 1963. Final Report on Enavid.
- Press Releases of the Committee on Safety of Drugs.
- Sherlock. Diseases of Liver and Biliary System, 3rd Ed., Publ. by Blackwell 1963, p.307.
- Eisalo et al. B.M.J., 1964, ii, 426 and 1965, i, 1416.
- Tyler. B.M.J., 1964, ii, 1264.
- Swyer and Little. B.M.J., 1965, i, 1412.
- Pincus et al. Am. J. Obst. Gynaec, 75, 1333.
- Aascher & Cuthbert. B.M.J. 1964, ii, 688.

DIAGNOSTIC PROBLEM (from page 31)

Diagnosis :

Adrenocortical hyperfunction. Confirmed by the finding of an elevated cortisol secretion rate together with high levels of urinary 17-hydroxycorticosteroids. In addition the diurnal variation of plasma 17-hydroxycorticosteroids was found to be absent although the absolute values were just within the upper range of normal.

To determine the site of the underlying pathological lesion, the full range of available tests was carried out. Space precludes their

discussion here, but in the event the most telling evidence was provided by a presacral aerogram which disclosed the presence of an abnormally enlarged right adrenal gland. Right adrenalectomy was carried out with the removal of a 28 G. cortical adenoma. Some difficulty was subsequently experienced in discontinuing exogenous steroid therapy, but otherwise the patient made an excellent recovery with resolution of all presenting complaints together with restoration of blood pressure to normal levels.