EVALUATION OF THE LOW DOSAGE ORAL CONTRACEPTIVE «WY—3707» (*)

by

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The wold wide acceptance of oral contraceptives as a means of family spacing has stimulated tremendous advances and investigations. Extensive studies with various steroid sex hormones have lead to the development of newer and more potent progestagens with reduction in the dose of the agent.

These new compounds have lessened the incidence of undesirable reactions without altering thair effectiveness.

The following is a report of study of a compound with minimal effective dosage suggested for maintaining potent fertility control.

MATERIAL

The investigation was started in January 1967, to study the effectiveness and any possible side effects of such preparation.

The structural formula of Wy-3707 is

(±) 13-β-Ethyl-17-α-ethinyl-17-hydroxygon-4-en-3-one

resembling norethisterone in certain structural characteristics but possesses a unique angulated methyl group, the latter seems to confer potent progestational properties which are evident even at low dosage.

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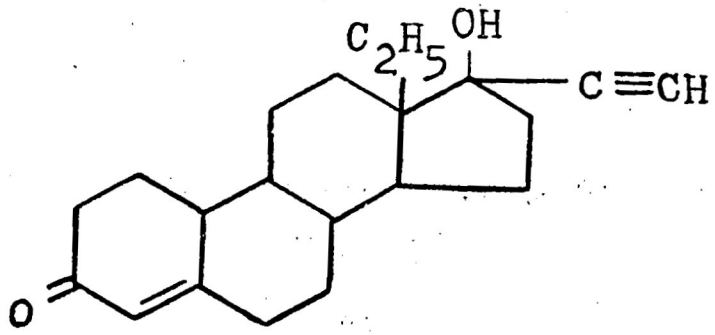

The pills contain each 0.5 mg. of the above mentioned compound together with 0.05 mg ethinyl oestradiol.

METHOD

The women for this study were seeking advice for family planning. They were women from the out-patient clinic of Ain Shams University hospital and from the author's private practice. Thus they are a mixture of all economic strata. At the initial visit a detailed medical history and clinical examination including pelvic examination were done all subjects before they were placed on medication. The majority (93%) were not using oral contraceptives for the last two months.

The number of patients subjected to study were :

200 outpatient clinic and

80 private patients

All with an age ranging from 20—40 years. The patients were given the pills for the first time on the 5th day of the cycle it has been recommended that an additional method of contraception during the first week of the starting cycle has to be used. They are given 21 tablets for a period of 3 weeks, then they go on with no pills for one week, During such a time menstrual flow usually occurs. On the 28th day, i. e. after 4 weeks, they were asked to report back and to start another course of 21 pills.

This rhythmic intake of three weeks and one week rest has made the method more simple and not easy to forget. With every subsequent visit (28 days period) the subjective complaints of the patients, their weights and blood pressure were recorded.

After 6 months from the start of the study,

60 cervical mucus tests and

30 endometrial biopsies were performed.

The cervical mucus tests have been done one week after the intake of the pills, while the endometrial biopsies were taken one week and also three weeks after the in take of pills.

RESULTS AND SIDE EFFECTS

The study had started with 280 patients and ended with almost 200 women. The drop out was 80 patients, 56 in the outpatient category and 24 of the private clinic patients. Thus the number of cycles in the study is, 1425 (Table I).

TABLE I

	Number of patients			No. of cycles
	Start	Drop out	Actual study	
Out patients	200	56	144	898
Private patients	80	24	56	527
Total	280	80	200	1425

It seems that the number of drop outs had falsely increased because of June war with almost cessation of the working clinics for few weeks and consequent defaultation of the patients. Actually very few patients ceased to have the pills because of side effects as will be mentioned later.

Not a single woman with this scheme of intake has shown to become pregnant and this above all proved its potent fertility control.

ANALYSIS OF RESULTS

Menstrual flow.

Rhythm.—had been regular all through because cycles were kept constant 28 days each.

Amount.—was average with no change in 124 cases i. e. 62%. It was diminished in 67 patients i. e. 33.5% and was increased in 9 patients i. e. 4.5%. No amenorrhoea was reported by any patient receiving the drug.

Duration of flow.—ranged from 1—7 days with an average of 4.08%. The flow usually followed 2—7 days from cessation of intake of pills with an average of 3.4 days.

Painful menstruation.—occurred in 6 cases i. e. 3%, in contradistinction to 22 patients (11%) prior to therapy.

Intermenstrual bleeding.—seven patients developed intermenstrual spotting and three patients developed actual break through bleeding, a total of 10 patients (5%). The majority of these cases occurred in the early cycles (60%).

TABLE II

		Numbers of patients	percentage
Rhythm	Regular	200	100%
	Irregular	—	—
Amount	Average	124	62%
	Diminished	67	33.5%
	Increased	9	4.5%
	Amenorrhoea	—	—
Painful menstruation	Befor intake	22	11%
	After intake	6	3%
Inter-menstrual bleeding	Spotting	7	3.5%
	Breakthrough	3	1.5%
	Total	10	5%
Duration of flow	ranged from 1—7 days (average 4.08%) following the cessation of pills by 2—7 days (average 3—4 days).		

One of those developing break through bleeding had been examined by speculum to show an irregular papillary cervical erosion. Papanicolaou smear and cevical biopsy were negative for malignancy and she resumed the intake of pills.

Weight changes :

96 patients (48%) had gotan increase in weight from 1—7 Kg. (average 2.4 Kg.)

No change in weight in 90 patients i. e. 45%.

A decrease in weight was reported in 14 patients i. e. 7% with an average of 1.8 Kg.

TABLE III

	No. of patients	percentage	Weight change in Kg.
Increased weight	96	48%	1—7 (average 2.4 Kg)
Decreased weight	14	7%	1—7 (average 1.8 Kg.)
Stationary weight	90	45%	

Blood pressure :

Blood pressure was average in 162 cases (81%), an increase in both systolic and diastolic from 5—35 mm/Hg was found in 32 patients (16%).

Also a decrease of 5—15 mm/Hg of both systolic and diastolic in 6 patients (3%).

Cutaneous manifestations :

3 cases developed acne (1.5%), one case developed urticarial rash in the second cycle which disappeared on cessation of the drug to reappear again its use for another two consecutive cycles. So she stopped to use the drug and she was fitted with an I. U. C. D.

No breast change. (as regards their size)

Three patients with varicose veins had no illeffects or thrombosis inspite of its use.

A wide variety of complaints were found in not a few patients signifying the difficulty in evaluation of many of these subjective complaints.

No one knows what percentage of women in the general population complain of nervous attacks, drowsiness of headache.

Unless the argument is quite evident culminating in production of definite symptoms, little could be be known conclusively from subjective data.

8 cases (4%) got nausea and vomiting specially occurring in the first two cycles, because of which 2 cases had to drop out.

Drowsiness was present in 22 cases (11%). Headache was complained of in 29 cases (14.5%) 15 of whom had previous attacks of headache prior to pills. (7%) What is remarkable about headache is that it increases in frequency in later cycles in contradistinction to nausea and vomiting.

Nervous tension was present in 5 cases (2.5%) because of which 4 stopped the intake of pills. Lactation was suppressed in all 22 patients receiving the drug leaving no doubt about such side effect.

No change in libido except one patient who insisted to attribute the marked diminution of libido to the drug and stopped using it. (Table IV).

Cervical mucus :

Of the 60 specimens taken one week after the intake of pills (i.e. 10th—12th day of the cycle).

53 cases showed absence of the Fern

5 cases had weak Fern and

2 cases had a definite positive Fern. (Table V).

TABLE IV

		No. of patients	Percentage
Blood pressure.	average	162	81
	increase	32	16
	decrease	6	3
Cutaneous manifestation	3 acne 1 urticariea		2
Breast size		—	—
Thrombosis		—	—
Nausea and vomiting		8	4
Drowsiness		22	11
Headache		29 (14) (15 had previously headache)	14.5 (—7%)
Nervous tension		5	2.5
Lactation		22 (all the lactating)	100
Libido		1	0.5

TABLE V

Fern test	No. of cases	percentage
Negative	53	88.3
Weakly positive	5	8.3
Strongly positive	2	3.3

Showing the results of Fern test in 60 specimens of cervical mucus.

Endometrial biopsy (Table IV)

10 biopsies were taken one week after intake of pills and showed precocious secretion in all except 2 cases which were peoliferative.

20 biopsies were done three weeks after intake of pills showed endometrial suppression evidenced by involution of the glands,

predecidual stromal reaction,

arterioles not well developed i.e. exhausted late secretory phase. The findings were almost uniform.

TABLE VI

Date of biopsy	Number	Description
1 week after intake of pills.	10	8 showed precocious secretion 2 were proliferative
3 weeks after intake of pills.	20	endometrial suppression shown by involution of the glands predecidual stromal reaction arterioles not well developed. i.e. exhausted late secretory phase. This findings were uniform.

DISCUSSION

It is well accepted that the mode of action of these steroids in the control of fertility is by suppression of the anterior lobe of the pituitary gland with inhibition of gonadotrophin secretion and consequently blocking ovulation.

The ovaries are at rest so there is no follicle maturation and no production of oestrogen and since no ova are produced, progesterone is not elaborated.

This has been compared to the physiological state of pregnancy during which ovulation is suppressed.

Normal menstruation does not occur but cyclical withdrawal bleeding is induced by periodic adminstration of the steroids and consequently the articificial menses thus brought on may be more regular than the spontaneous cycles. The oestrogenic component of the gestagen in mainly responsible for the inhibition effect of the adenohypophysis. Also progestagens are reported to produce changes in the cervical mucus that cause a hostile barrier to the survival and migration of sperms.

It has been pointed out that additional factors may contribute to the role of gestagen in prevention of conception. Thus attempts to stimulate ovulation with human pituitary F.S.H. and human chorionic gonadotrophins while the patient on steroid medication in the usual dose for contraception regimen have met with failure pointing to the valid possibility of the direct effect of gestagens on the ovary-through blocking its ability to respond to gonadotrophins. This is to be induced via the enzymatic metablic block mechanisms.

All these state of affairs are fortunately reversible after withdrawal of the gestagen but no body has got more than educated guess for the various permanent effects on the pituitary, ovaries and uterus not to mention the other well known side effects specially after years of prolonged use.

Hence advances in studies of steroids tend to discover effective smaller dosage of progestagen with the least likehood of production of undesirable effects. Wy-3707 compares very favourably with any other known produced gestagen.

The clinical experience reported indicates the 100% reliability of this smaller dose gestagen in birth control.

The scheme of adminstration of three weeks on pills and one week off has made the method of use more simpler and regular. The incidence of side reactions in gratifying and is much less than with other gestagens used for contraception (containing 2—20 times the progestagen component and 1—3 times oestrogen component) as shown in table VII (B.M.J. 1964/11).

TABLE VII

Product	No. of patient	No. of cycles	% of nausea in 1st. cycle	% of preg-nancy	% of head-ache	% of amenorr-hoea
Lyndiol	170	2035	40	0	5	5
Orrhonovin	114	1106	29	0	4	0.5
Norlestrin	153	1377	32	0	6	3
Gynovlar	96	433	12	0	4	1
Ovulen	26	245	20	0	4	1
Wy-3707	200	1425	4	0	7	0

Nausea, headache, nervousness, fluid retention, weight gain and skin changes, constituted the majority of side effects although they were responsible for minimal withdrawal.

As it was suggested June war had disturbed earlier part of study, discontinuation of the work in clinics during this time is the main cause for the 80 patients withdrawal. Those patients who returned after, had carried on the intake of pills and constitute the bulk of this study and the drug wide acceptability is attested by the very small percentage of patients withdrawing later from the program for reasons attributable to its use.

Acceptance and effective use of any method depend also on motivation for control of conception. Motivation and desire are in turn determined by many complex factors, above all is high parity and socioeconomic status together with others. More knowledge is needed before this problem can be dealt with successfully. Patients with strong desire to limit fertility require little support to overcome any unpleasant manifestation.

The rather uniform and adequate pattern of 20 endometrial biopsies after use of pills is responsible for the regular withdrawal menses where too mature endometrium showing involution of glands

generalised suppression prevents proper nidation of ovum even if it is present and also explaining the rarity of breakthrough bleeding one of the deterants to the pill use.

The innumerable benificial results of Wy-3707 for contraception for outweigh its small percentage of undesirable effects.

SUMMARY

1. Pills containing 0.5 mg new progestagen Wy-3707 + 0.05 mg ethinyl oestradiol were adminstered for three weeks and one week off for 280 patients for a total of 1425 cycles.

2. During the period of adminstration, no pregnancy was ever recorded while taking these tablets as prescribed.

3. Undesirable effects were infrequent sufficiently, very mild, and less annoying with these tablets, resulting in minimal withdrawal for this reason.

REFERENCES

1. Behrman, S. J., Obstet. Gynec. 24 ; 101, 1964.
2. Board, J. A., and Borland, D. S., Obstet. Gynec. 24 : 655, 1964.
3. Cook, H. H., Gamble, C. J., and Salterthwaite, Amer. J. Obstet. Gynec. 82, 438, 1961.
4. Durkin, J. W., «Lin. T. J. and Kim, Y. J., Amer. J. Obstet. Gynec. 91 : 110, 1965.
5. Eckstein, P., Waterhouse, J. A. H., Bond, G. M., Mills, W. G., Sandlands, D. M., and Shotton, D. M., Brit. Med. J. 2 : 1172, 1961.
6. Garcia, C. R., Pincus, G., and Rock, J., Amer. J. Obstet. Gynec. 75 : 82, 1958.
7. Newland, D. O., Marshall, L. L., and Webber, R. L. Amer. J. Obstet. Gynec., 23 : 920, 1964.
8. Roberts, J. S., Brit. Med. J. 11 : 8732, 1964.
9. Roland, M., Clyman, M. J., Decker, A., and Ober, W. B. Fertil. Steril. 14 : 402, 1963.
10. Rovinsky, J. J., Obstet. Gynec. 23 : 840, 1964.
11. Ryan, G. M., Craig, J., and Reid, D. E., Amer. J. Obstet. Gynec. 90 : 715, 1965.
12. Suran, R. R., Fertil. Steril, 18 : 598, 1967.
13. Yen, S. C., Fertil. Steril. 16 : 97, 1965.
14. Zell, J. R., and Crisp, W. E., Obst. Gynec. 23 : 657, 1964.