residual follicle stimulating hormone secretion leading to the production of polycystic ovaries (Ferriman, 1960); all follicle stimulating hormone secretion may have disappeared in the more severely affected patients. The development of sensitive and precise radio-immunological assays for gonadotrophins may shed some light on the problem before long.

The incidence of conception in our series (9 out of 41) is higher than we would have anticipated from our previous experiences in the field. This has been the experience of many other workers (Greenblatt, 1966). It is not possible to make a precise statistical assessment of the comparative value of this drug in the absence of control data. The provision of such data would be of great interest.

It is odd that while patients with polycystic ovaries show a better ovulatory response to clomiphene than those with normal-sized ovaries their conception rate should be lower. Perhaps the thickened capsules of the polycystic ovaries interfere with the release of ova, or the increased production of androgen by these ovaries impairs nidation.

Summary

The ovulatory response to clomiphene is significantly better in patients with menstrual cycles of less than six months' duration compared with those whose cycles exceed this figure, and in patients with polycystic ovaries compared with those whose ovaries are of normal size. It is better in patients with basal oestrogen excretions exceeding 21 μg./24 hours than in those whose excretion levels fall below this figure (obtained by a method having a nonspecific background fluorescence of 10 μg./24 hours), though the difference does not quite reach formal significance.

Patients with normal-sized ovaries conceive more readily than those with polycystic ovaries. The difference does not quite reach formal significance.

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Current Concepts in the Treatment of Anovulation

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When mechanical or anatomical lesions are excluded, disturbances of ovulation and corpus luteum function represent the main cause of infertility.

The factors which disturb the proper function of the reproductive system from within may stem from any of the participating cells or populations of cells in the central nervous system, the pituitary gland, the ovary, or perhaps even the uterus. These factors may involve faulty stimulation (abnormal magnitude, sequence of appearance, or time of action of stimuli) or faulty response of the target cells or organs. Each and every one of these factors, if sufficiently powerful, or when acting long enough, may lead to an imbalance of the hormonal feedback mechanism and consequently to impaired fertility. In the majority of cases some absolute or relative primary or secondary abnormality in the nature or magnitude of gonadotropic stimulus exists, regardless of the primary cause. A convenient simplification is to divide these patients into two groups: those with gonadotropic insufficiency due to primary failure in production of gonadotropins, and those with abnormal gonadotropic stimulus due to disturbed release of gonadotropic hormones.

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Preparations of human gonadotropins and clomiphene citrate have proved to be of definite value in the treatment of these two groups of patients.

Recently gonadotropic extracts from human post-mortem pituitaries and human menopausal urine have been made available for clinical use. These preparations in conjunction with human chorionic gonadotropins have proved capable of inducing ovulation. Numerous pregnancies have resulted from such treatment (Gemzell, 1966; Lunenfeld and Donini, 1966; Shearman, 1966; Rabau *et al.*, 1967). It was shown by Crooke *et al.* (1963) and Diczfalusy *et al.* (1964) that gonadotropic preparations derived either from human post-mortem pituitary glands or from postmenopausal urine, administered to the same patients, provoked a similar response as judged by steroid excretion patterns and by vaginal or endometrial morphology.

Another approach to the treatment of anovulation was made possible by the introduction of clomiphene citrate (MER-41). This synthetic non-steroid preparation is a derivative of chlorotrianisene (TACE) and possesses both oestrogenic and anti-oestrogenic properties (Greenblatt, 1966). The exact mechanism of action of clomiphene in inducing ovulation is as yet unclear. Since urinary excretion of gonadotropins was reported to be increased during or immediately after administration of clomiphene (Dickey *et al.*, 1965), it has been suggested that the drug acts either directly or indirectly on

the release of gonadotropins. There is, however, no general agreement whether clomiphene causes the release of follicle-stimulating hormone (F.S.H.) (Kistner, 1966), luteinizing hormone (L.H.) (Igarashi *et al.*, 1967), or both (Dickey *et al.*, 1965). Whatever the exact nature of its action, clomiphene citrate has been shown capable of inducing ovulation in certain types of anovulatory patients (Johnson *et al.*, 1965 ; Greenblatt, 1966 ; Kistner, 1966 ; Serr *et al.*, 1966 ; Shearman, 1966).

Principles and Results of Treatment

Human gonadotropins or clomiphene citrate were administered to 235 patients through 761 courses of treatment. The patients were divided into two main groups according to the level of gonadotropins and to the endogenous oestrogen activity as judged by urinary oestrogen, vaginal smears, cervical mucus, and/or occurrence of withdrawal bleeding following administration of medroxyprogesterone acetate (MAP).‡ The two main groups were subsequently subdivided according to the clinical signs, such as amenorrhoea and other ovulatory disturbances as outlined in Table I. Patients who had low urinary gonadotropins and no detectable oestrogenic activity were treated by human gonadotropins ; those with urinary gonadotropins within the normal range and evidence of endogenous oestrogen activity (MAP-positive) were given either gonadotropic preparations or clomiphene citrate ; cases diagnosed as corpus luteum insufficiency were treated with clomiphene only, and formed a separate group (group III).

TABLE I.—*Number of Cases and Treatment Courses in Various Groups of Patients With Ovulatory Failure*

	No. of Cases	No. of Treatment Courses
Group I (low gonadotropins, no evidence of endogenous oestrogen activity):		
Primary amenorrhoea	27	52
Secondary „	65	127
Post-partum amenorrhoea (Chiari-Frommel syndrome)	7	9
Sheehan's syndrome	1	1
Group II (gonadotropins in normal range, evidence of endogenous oestrogen activity):		
Secondary amenorrhoea	18	53
Follicular phase disturbances (oligomenorrhoea)	34	105
Polycystic ovary syndrome (histologically proved)	6	29
Anovulation with fairly regular cycles	31	83
Group III (corpus luteum insufficiency)	46	302
Total	235	761

Dosage, Treatment Schedules, and Results of Gonadotropic Treatment

Human menopausal gonadotropin (H.M.G.)§ having both follicle-stimulating and luteinizing activities was used. Each ampoule of the preparation contains approximately 75 i.u. of F.S.H. and 75 i.u. of L.H. Each treatment course was scheduled according to the patient's individual response. Treatment was started with H.M.G. (Pergonal) at a dose varying from 1 to 4 ampoules per day. Follicle maturation and oestrogen secretion were evaluated from urinary oestrogen levels, crystallization of cervical mucus (ferning pattern), the appearance of external cervical os, vaginal smears, and ovarian size. Treatment was continued until oestrogen secretion, as evidenced by the response of these target organs, was somewhat greater than during the peak of a normal preovulatory phase.

‡ Progestational agent with no intrinsic oestrogenic activity.
§ Supplied as Pergonal by Istituto Farmacologico "Serono," Rome, Italy, and later by Ikapharm, Ramat-Gan, Israel.

Administration of human chorionic gonadotropin (H.C.G.)‖ was then started. Pergonal was usually continued during the first two days of H.C.G. administration, which was given in a dose of 5,000–10,000 i.u. daily for three to four days. The patients were instructed to have intercourse on each of these days.

Diagnosis of ovulation was regarded as proved only if pregnancy ensued. The occurrence of ovulation and the presence of a functioning corpus luteum were, however, presumed on the basis of the following criteria: basal body temperature shift, progestational changes in vaginal smears, disappearance of previously strong positive ferning pattern, urinary pregnanediol excretion of at least 2 mg./24 hours, secretory changes in the endometrium, and menstrual bleeding appearing 13 ± 2 days after the presumed day of ovulation.

Table II shows the results of sequential H.M.G.-H.C.G. therapy. Most of the patients responded to treatment with doses varying up to 50 ampoules of Pergonal and 25,000 i.u. of H.C.G. Only in a few cases were higher doses needed to produce the desired effect. Statistical evaluation showed a significant correlation between the nature of the hormonal disturbance and the quantity of H.M.G. required for ovulatory response. Patients with amenorrhoea needed significantly more Pergonal than those with follicular phase disturbances (oligomenorrhoea) and anovulation ($P<0.001$). Whether these differences in response were caused by differences in ovarian sensitivity to gonadotropins or were related to the effect of the patient's endogenous feedback mechanism is as yet unknown.

TABLE II.—*Results of Sequential H.M.G.-H.C.G. Treatment in* 134 *Patients* (1961–6)

	No. of Cases	No. of Courses	Courses per Patient	Presumed Ovulation		Pregnancy		
				No.	% of Courses	No.	% of Patients	% of Courses
Group I								
Primary amenorrhoea	27	52	1·9	43	82·6	17	62·9	32·7
Secondary „	65	127	1·9	114	89·7	41	63·0	32·3
Post-partum amenorrhoea (Chiari-Frommel syndrome)	7	9	1·3	9	100·0	6	85·7	66·6
Sheehan's syndrome	1	1		1		1		
Subtotal (group I)	100	189	1·9	167	88·3	65	65·0	34·4
Group II								
Secondary amenorrhoea	7	16	2·3	16	100·0	5	71·4	31·3
Follicular phase disturbances (oligomenorrhoea)	11	17	1·5	15	88·2	7	63·6	41·1
Anovulation with fairly regular cycles	16	34	2·1	26	76·5	3	18·8	9·0
Subtotal (group II)	34	67	1·9	57	85·0	15	44·1	22·4
Total	134	256	1·9	224	87·5	80	60·0	31·3

The overall abortion rate after treatment with H.M.G. and H.C.G. was 24%. Mild adverse reactions were noted in 4.2% and severe reactions (hyperstimulation syndrome) in 2.8% of patients. A detailed description of adverse reactions was reported elsewhere (Mozes *et al.*, 1965 ; Rabau *et al.*, 1967).

Dosage, Treatment Schedules, and Results of Clomiphene Treatment

One hundred and one patients were treated through 505 courses (Table III). The criteria of positive response were identical with those employed in gonadotropic treatment. As to the dosage schedules, numerous authors (Naville *et al.*, 1964 ; Dickey *et al.*, 1965 ; Kistner, 1965 ; Pildes, 1965 ; Serr *et al.*, 1966 ; Shearman, 1966) pointed out that lower dosage and shorter treatment resulted in a decrease of more serious side-effects related to ovarian overstimulation, while the overall pregnancy rate remained unaffected.

‖ Supplied as Chorigon by Ikapharm, Ramat-Gan, Israel.

We generally start with a dose of 50 mg. of clomiphene¶ daily for seven consecutive days. Only those patients who do not respond to this dosage (with either rise in basal body temperature or increase in urinary pregnanediol) are given 75 mg. daily for seven days. Those who still do not respond are then given a trial course of 100 mg. daily for the same length of time. If two trials with this latter regimen are ineffective the patient is classified as unsuitable for clomiphene therapy and is scheduled for treatment with human gonadotropins. Gonadotropic treatment after failure to respond to clomiphene has been used so far in five patients. Two of them conceived.

TABLE III.—*Results of Clomiphene Treatment in* 101 *Patients*

	No. of Cases	No. of Courses	Courses per Patient	Presumed Ovulation		Pregnancy		
				No.	% of Courses	No.	% of Patients	% of Courses
Group II:								
Secondary amenorrhoea	11	37	3·4	16	43·2	4	36·3	10·8
Follicular phase disturbances (oligomenorrhoea)	23	88	3·8	63	71·6	13	56·5	15·7
Polycystic ovary syndrome*	6	29	4·8	25	86·2	2	33·3	7·0
Anovulation with fairly regular cycles ..	15	49	3·3	36	73·4	8	53·3	16·3
Subtotal (group II) ..	55	203	3·7	140	68·9	27	49·0	13·3
Group III: Corpus luteum insufficiency (or anovulation with luteinization of follicles)	46	302	6·6	176	58·2	7	15·2	2·3
Total	101	505	5·0	316	62·6	34	33·6	6·7

* Proved by histology.

The overall abortion rate in patients treated with clomiphene was 20.6%. No serious adverse reactions were noted.

Discussion

Disturbance of ovulation is one of the main causes of sterility. The use of sequential H.M.G.-H.C.G. therapy and of clomiphene enabled induction of ovulation in a considerable number of anovulatory patients. A prerequisite condition for successful induction of ovulation is the presence of ovaries capable of response to stimulation. Therefore patients with ovarian agenesis or dysgenesis or with menopausal-like ovaries are unsuitable for this treatment. Since the action of clomiphene is mediated through the pituitary, in patients treated with this agent the presence of a pituitary gland capable of synthesizing gonadotropins is essential. We have divided patients with anovulation into two groups: those with primary failure in production of gonadotropins, and those with abnormal gonadotropic stimulus due to disturbed release of gonadotropic hormones. The latter condition may be caused either by a defect in the pituitary-hypothalamic complex or by abnormal ovarian feedback mechanism. Patients in group I present with primary or secondary amenorrhoea, low or undetectable gonadotropins, and absence of endogenous oestrogen production. Patients in group II have gonadotropins in the normal range (sometimes low), secondary amenorrhoea, oligomenorrhoea or anovulatory cycles, and evidence of endogenous oestrogen production. In group I cases substitution therapy by H.M.G. and H.C.G. is needed. Patients in group II may be treated with human gonadotropins or with clomiphene with a very similar success rate.

Since pregnancy is the main goal of treatment and the only unequivocal sign of ovulation, the results of treatment with human gonadotropins or with clomiphene should be analysed in relation to the pregnancy rate. Such an analysis shows that in our material sequential H.M.G.-H.C.G. therapy gave the best results in patients of group I, and the pregnancy rate obtained in group II was somewhat lower (65% and 44.1% respectively). The mean percentage of treatment courses resulting in pregnancy was significantly higher in group I (34.4) than in group II (22.4). The lower pregnancy rate in this latter group was due mainly to the poor results obtained in patients with anovulation associated with fairly regular menstrual cycles. However, it should be pointed out that these patients responded well to clomiphene treatment—53.3% of pregnancies. It might be speculated that in these cases the patient's feedback mechanism interferes unfavourably with gonadotropic treatment. Clomiphene, allowing a more flexible interplay between gonadotropic release and ovarian feedback, provides better results.

The overall results of clomiphene treatment in group II were similar to those obtained by gonadotropic therapy, 49.0% and 44.1% pregnancies respectively. It should be noted, however, that clomiphene required more treatment courses than sequential H.M.G.-H.C.G. administration. The mean number of courses per patient was 3.7 in clomiphene treatment and 1.9 in gonadotropic therapy. The percentage of treatment cycles resulting in pregnancy was 13.3 and 22.4 in clomiphene and gonadotropic therapy respectively. This may be due to the simpler but more rigid dosage scheme used in clomiphene treatment as compared with the flexible, individually adjusted treatment schedule of gonadotropic therapy.

Our results with clomiphene treatment show a pregnancy rate higher than that reported by other authors (Bishop, 1965 ; Johnson *et al.*, 1965 ; Beck *et al.*, 1966 ; Greenblatt *et al.*, 1966). This is probably due to preselection of patients.

In group III (corpus luteum insufficiency) clomiphene gave rather poor results. Pregnancy was achieved in only 15.2% of patients and in 2.3% of treatment courses. Sequential H.M.G.-H.C.G. given to a few patients produced even poorer results. Patients in this group differ from those in groups I and II because they show indirect signs of ovulation such as a rise in basal body temperature, disappearance of previously positive ferning pattern, progestational effect in vaginal smears, and some degree of secretory changes in the endometrium. Urinary pregnanediol excretion is above 1 mg./24 hours but rarely reaches normal values.

Oestrogen deficiency found in some of these patients during the follicular phase suggests that at least a part of this group represent anovulation with luteinization of unruptured follicles, rather than ovulatory cycles with insufficient corpus luteum function. It might be speculated that in these patients the disease is due to faulty response of the ovaries to gonadotropic stimulation. Detailed investigations of this group of patients are in progress.

On the basis of presented data it may be concluded that treatment with human gonadotropins and with clomiphene citrate is highly effective in sterility due to anovulation. When the patients are carefully selected for suitable treatment an overall pregnancy rate of 57% may be expected.

Summary

A series of 235 patients with infertility due to disturbances of ovulation were treated with human gonadotropins or with clomiphene citrate. The patients were divided into two main groups according to the level of urinary gonadotropins to the endogenous oestrogen activity. Patients with corpus luteum insufficiency formed a separate group. Group I (low urinary gonadotropins, no evidence of endogenous oestrogen activity) comprised 100 patients with primary, secondary, or postpartum amenorrhoea. Group II (gonadotropins in normal range, evidence of endogenous oestrogen activity) included 89 patients with secondary amenorrhoea, oligomenorrhoea, or anovulatory cycles. Forty-six patients with corpus luteum insufficiency formed group III.

¶ Generously supplied as Clomid by Wm. Merrell Co., U.S.A., and later as Ikaclomin by Ikapharm, Israel.

Patients of group I were given sequential H.M.G.-H.C.G. therapy, those of group II received either gonadotropins (34 cases) or clomiphene (55 cases), and those of group III were treated with clomiphene only.

Gonadotropic therapy gave better results in patients of group I than in those of group II (65% and 44.1% of pregnancies respectively). In group II patients gonadotropins and clomiphene gave similar results (49% and 44.1% pregnancies respectively). The results in group III were poor (15.2% of pregnancies).

When patients are carefully selected for suitable therapy, sequential H.M.G.-H.C.G. or clomiphene therapy provides an overall pregnancy rate of approximately 57%.

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Three Swedish Families with Porphyria Variegata*

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The interest in porphyrins and porphyria diseases has increased considerably during the last decades. This fact is probably partly due to the great progress made in porphyrin chemistry during that time.

In Sweden porphyria acuta intermittens (PAI) is predominant among the diseases with disturbances in the porphyrin metabolism. One of us (Waldenström) has studied this disease and its spread in our country during the last 35 years. About 600 cases are now known, half of them still living. Careful genetic studies have revealed a non-sex-linked inheritance of Mendelian dominant type. Clinically the classical symptoms are, first, severe abdominal pain which may lead to operations with fatal outcome; psychiatric symptoms, varying from short periods of confusion to severe psychosis, where sedating drugs aggravate the state; and neurological manifestations such as coma or epileptic fits, and above all pareses, including respiratory paralysis, which has often been the cause of death. We do not know of any clear-cut PAI patient with light-sensitivity. Chemically the typical findings in PAI are increased urinary excretion of porphyrin precursors—that is, porphobilinogen (PBG) and δ-aminolaevulic acid (ALA). The disease has therefore been designated as pyrrholia or pyrrholoporphyria. The latent cases were found by analysis of PBG in the urine (Waldenström, 1937). The faecal excretion of porphyrins is only slightly increased or not at all increased (Haeger-Aronsen, 1962). The absence of preformed porphyrins inside the body has been regarded as the explanation of the lack of light-sensitivity.

Among the white population in South Africa a great number of patients have been shown to have a special type of porphyria (Dean, 1953; Dean and Barnes, 1955, 1958; Eales, 1956, 1960). Clinically, all the symptoms typical of PAI may be present, often with light-sensitivity. In many cases only the skin is affected. As in PAI, the inheritance is dominant, non-sex-linked. Because of the varying symptoms the disease was given the name porphyria variegata (PV) by Dean and Barnes (1959). The best way to find the latent cases of this disease is to analyse the faecal excretion of porphyrins, which is almost always markedly increased. It has been claimed that only during the acute stage is the PBG and ALA excretion in the urine pathologically increased. At first the difference between PAI and PV regarding cutaneous symptoms was supposed to be due to the higher intensity of sunlight in Africa. However, the different biochemical characteristics mentioned above and the appearance of PAI in South Africa with signs and symptoms quite typical and without genetical connexion with PV (Dean, 1963) supported the earlier opinion of Waldenström that PAI and PV were two different gene defects. Dean and Barnes (1959) confirmed this statement once and for all.

Earlier, 13 Swedish cases from four different families with porphyria variegata or protocoproporphyria were reported (Waldenström and Haeger-Aronsen, 1963). We suspected that these cases, of which five were latent, represented PV, since one from each family suffered from light-sensitivity and several cases had considerably higher faecal excretion of porphyrins than is usually seen in PAI. The only case which fulfilled all the criteria so completely that the diagnosis PV could be made with certainty was that of a Danish woman (Case 3).

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