

The use of Clomiphene Citrate in the treatment of infertility

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IT USED to be only of academic interest to find out if the woman is ovulating in the investigation of infertility. As ovulation can now be successfully induced, it is important to determine the presence or absence of ovulation, and the frequency and regularity of ovulation if it is present.

Ovulation was successfully induced in the human by Gemzell, Diczfalusy and Tillinger with human pituitary gonadotrophin in 1958, by Kistner and Smith with MER 25 in 1960, by Lunenfeldt, Menzi and Blaise with gonadotrophin extracted from the urine of postmenopausal women in 1960 and by Greenblatt, Barfield, Jungok and Roy with clomiphene citrate in 1961.

Clomiphene citrate is an analogue of the non-steroid oestrogen, chlorotrianisene. Its precise method of action in the human female is still unknown. There may be two separate and independent actions. Firstly, it may stimulate the pituitary and probably the hypothalamus by displacing oestrogen, and hence removing the inhibitory effect of oestrogen, in these areas. Secondly, it may act directly on the enzyme systems involved in steroidogenesis in the ovary, reducing cytochrome-C reductase and making TPNH more available for the aromatisation reaction, thus increasing secretion of oestradiol and oestrone.

Kistner in 1965, from an analysis of 1,731 individual case reports, showed that 1,211, or about 70 per cent, had one or more apparently ovulatory cycles and that 333 or about 19 per cent (or 28 per cent of those with ovulatory response) subsequently became pregnant. In summarising the results of various clinical trials on 2,616 cases, Johnson, Bundle and Hoekenga (1966) reported apparent ovulation in 1,809 cases or 69 per cent and subsequent pregnancy in 429 or 16 per cent.

A Report on 4 Patients treated with Clomiphene Citrate

During the period of one year, from August 1968 to July 1969, four patients had been treated with clomiphene citrate at the University Hospital, Kuala Lumpur. Some of their salient clinical features are summarised and presented in Table I.

The first patient, aged 31, presented with primary infertility for 3½ years and amenorrhoea for 2 years, during which she would have a menstrual flow only if she had been given some hormonal pills or injections. She had also put on 15 pounds. Physical examination and laboratory investigations confirmed the diagnosis of sclerocystic ovarian syndrome (Stein-Leventhal syndrome) and excluded the presence of other causes

Table I
A Summary of the Report on 4 Patients treated with Clomiphene

Patient	Age	Presenting Symptom	Menstrual Cycle	Dose and Number of Course	Response
1	31	Primary infertility for 3½ years	Amenorrhoea for 2 years	250 mg. x 2	Ovulation
2	32	Primary infertility for 6 years	4-5/2-8 months	500 mg. x 2 700 mg. x 1	Pregnancy
3	27	Primary infertility for 3½ years	5-7/4-9 weeks	250 mg. x 2 500 mg. x 1 500 mg. x 3	Pregnancy Pregnancy
4	32	Secondary infertility for 3 years	4-5/6-16 weeks	250 mg. x 2 500 mg. x 1	Pregnancy

of infertility and that of other endocrine pathology. She was first seen in May, 1968 and had two episodes of spontaneous menstrual flow in June and August, 1968 respectively. Basal body temperature record, however, did not show any biphasic pattern. She was given two courses of clomiphene citrate, each course consisting of 50 mg. daily for 5 days. Since then, she had been menstruating regularly at 28 days' interval and biphasic curves were consistently shown in the basal body temperature record. She was, however, still unable to have a pregnancy.

The second patient presented with primary infertility for 6 years. She had very irregular and infrequent periods, the intervals varying from 2 to 8 months. She and her husband were investigated for infertility in another hospital, and other than the anovulatory cycles, nothing abnormal had been found. She had already been given two courses of clomiphene citrate before she sought advice at the University Hospital. The first course of clomiphene citrate, 100 mg. daily for 5 days, was started on 27th August, 1968. The basal body temperature showed a biphasic pattern and she had a menstrual flow from 27th to 29th September, 1968. The second course of the same dosage was started on 1st October, 1968. The basal body temperature remained persistently low and she did not have a period in early November. The third course of 100 mg. daily for 7 days was commenced on 14th November, 1968. The basal body temperature record showed a dip and then a rise

of temperature on 30th November, 1968 and the temperature remained elevated. Pregnancy was confirmed and followed a normal course. She had a normal spontaneous fulltime delivery on 8th August, 1969. The normal female baby weighed 2890 grams at birth.

The third patient presented with primary infertility for 3½ years and irregular and infrequent menstrual periods, the intervals varying from 4 to 9 weeks. Basal body temperature record revealed the presence of occasional and infrequent ovulation. No other causes of infertility could be found. She was given 3 courses of clomiphene citrate, 50 mg. daily for 5 days in each course, and each was followed by a biphasic curve of the basal body temperature and also by a normal menstrual flow 4 weeks after the commencement of the course. In the third course, the dosage was increased to 100 mg. daily for 5 days and she became pregnant as evidenced by the following observations: persistently raised basal body temperature, positive pregnancy test, nausea and frequency of micturition and an enlarged and soft uterus. Unfortunately, she had a complete abortion 10 weeks after her last normal menstrual period. Starting from 6 weeks after the abortion, 3 more courses of clomiphene citrate were administered (100 mg. daily for 5 days). She became pregnant again after the third (or the sixth for this particular patient) and she was given intramuscular injection of progesterone (100 mg. daily) till the 10th week and proluton (500 mg.

weekly) till the 20th week. At the time of report, she was 25 weeks pregnant and satisfactory progress was being made.

The fourth patient presented with infertility following an abortion which took place 3 years previously. She also had very irregular and infrequent menstrual periods, the intervals varying from 6 to 16 weeks. The basal body temperature record, however, showed the presence of a rise in temperature for 12 to 14 days before each menstrual flow. As no other abnormalities could be found, she was given 3 courses of clomiphene citrate (2 courses of 50 mg. daily for 5 days and the third of 100 mg. daily for 5 days). She was pregnant after the third course but unfortunately, the pregnancy terminated in abortion 14 weeks after the last normal menstrual period. As the patient had to leave the country, no further course was given.

Discussion

Correct selection of the patient is important as clomiphene citrate should be given only when it is indicated. As infertility is very often the chief complaint, various investigations, including seminal analysis and tests for tubal patency, should be carried out. Clomiphene citrate should be seriously considered for patients having oligomenorrhoea (or even amenorrhoea after ruling out an organic lesion in the hypothalamus or pituitary and ovarian dysgenesis) or anovulatory (or largely anovulatory) menstrual cycles (as in Cases 1, 2 and 3). Clomiphene citrate should also be considered for patients having ovulatory menstrual cycles which are very irregular and infrequent. Increasing the frequency of ovulation and correct timing of intercourse should increase the chance of pregnancy (as in Case 4). Most investigators are of the opinion that patients with sclerocystic ovarian syndrome (Stein-Leventhal syndrome) usually exhibit an ovulatory response to clomiphene (as in Case 1).

No side effects have been noted in these four patients following the administration of clomiphene citrate. Ovarian enlargement has been found in 2.7 per cent to 7.8 per cent of patients taking clomiphene citrate, depending on the duration of therapy. It is, therefore, recommended that careful pelvic examination be performed before each course of clomiphene therapy, with particular attention being given to the size of the ovaries. As the ovaries of some patients with sclerocystic ovarian syndrome are more sensitive to the stimulatory effect of clomiphene, greater precautions need to be taken. A higher dosage of clomiphene might succeed to lead to a pregnancy as

in Case 1. This had not been given because her ovaries were slightly enlarged even before the therapy and also because she was living and working in another town, and thus it was difficult to keep her under close and constant supervision.

Two courses of 250 mg. for each course (50 mg. daily for 5 days) have led to regular ovulatory menstrual cycles in Case 1. Whilst the first course of 500 mg. (100 mg. daily for 5 days) in Case 2 led to ovulation, the second course of the same dosage failed to do so. But when the third course of 700 mg. (100 mg. daily for 7 days) was given, the patient succeeded to have a pregnancy which ended in a normal spontaneous delivery. Whilst it is important in principle to use the minimal effective dose (so as to reduce the incidence of side effects, such as ovarian enlargement and multiple pregnancy), it is interesting to note that in both Cases 3 and 4, when a course of 250 mg. invariably produced ovulation, pregnancy only occurred when a course of 500 mg. was given.

Of the 12 patients treated with clomiphene citrate by Townsend et al (1966), ovulation was successfully induced in 9, and 3 became pregnant. Of 191 patients treated with clomiphene citrate by Osmond-Clarke et al (1968), 134 (70 per cent) had a clinical response (menstruation with evidence of ovulation); and of the 104 patients who responded to treatment and who also complained of infertility, 39 (37.5 per cent) became pregnant. Van Hall and Mastboom (1969) treated 27 women, of whom 18 also complained of infertility, with clomiphene citrate without a single pregnancy. Whilst ovulation was successfully induced in all the four patients in the present report, there were 4 pregnancies among 3 of the patients.

Even though it was an accepted fact that the incidence of abortion was higher among patients who gave a history of infertility, it was most disappointing to observe that 2 of the 4 pregnancies had ended in abortion. Supportive hormonal therapy probably should have been instituted as soon as pregnancy was confirmed. Goldfarb and Crawford (1969) gave their patients medroxyprogesterone and ethinyl oestradiol (20 mg. of the former and 100 ug. of the latter daily by mouth from the diagnosis of pregnancy till the 10th week and then 30 mg. and 150 ug. respectively daily till the 20th week). Of the 160 patients treated with clomiphene citrate by them, there were 37 pregnancies all of which were given supportive hormonal therapy. There were only 4 premature labours and 3 abortions.

The importance of carefully and accurately recording the basal body temperature cannot be over-

emphasised. It is the most practical method which can be used in any centre. It does not only show the presence of ovulation but also its time. And if a definite relationship between the first day of the last menstrual period and the time of ovulation can be shown by a recording of temperature over a few cycles (spontaneous or induced by clomiphene citrate), advice can then be given to the couple as regards the most appropriate time for intercourse to take place. The basal body temperature chart will also show the duration of the luteal phase. Although there is no evidence to suggest that clomiphene either increases the rate of abortion or the incidence of congenital malformations, the administration of this compound during early pregnancy should be avoided by recording the basal body temperature, looking for symptoms and signs of pregnancy and asking for pregnancy tests. On the other hand, absence of menstrual flow does not necessarily imply pregnancy, and, without a carefully kept basal body temperature record, the administration of yet another course of clomiphene citrate in higher dosage may be unduly delayed. The usefulness of the basal body temperature record in this respect has been well illustrated by Case 2.

SUMMARY

After a brief review of the literature, four patients treated with clomiphene citrate for infertility at the University Hospital, Kuala Lumpur, were reported.

The use of clomiphene citrate in the treatment of infertility is then discussed under the following headings: selection of patients, side effects, dosage, pregnancy, abortion and basal body temperature record.

Addendum:

After the submission of the article, the first patient (case No. 1) presented herself at the out-patient clinic and was then found to be 16 weeks' pregnant.

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