Low-Dosage Clomiphene Therapy in the Treatment of Infertility due to Defective Ovulation

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SUMMARY

The use of clomiphene in gradually increasing doses, in cases of infertility due to anovulation, oligo-ovulation and inadequate luteal phase, led to a high pregnancy rate, particularly in the initial stages of treatment. Although clomiphene is a relatively safe and inexpensive drug, there is a possibility that high doses in repeated cycles may adversely affect fertility by its anti-oestrogenic effect. It is therefore suggested that therapy be commenced with a lower dosage than that generally recommended.

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At the 46th South African Medical Congress held in Durban in July 1967, Dr Robert Kistner presented a paper entitled 'Induction of ovulation with clomiphene citrate (Clomid)'. Exciting prospects were opened for infertile couples with the anticipated availability of this new drug.

The precise method of action of clomiphene in the human female is unknown. Initially it was thought that the primary action of clomiphene was either directly upon the enzyme systems involved in ovarian steroidogenesis or as a potentiator of gonadotrophins. More recent studies[1] have suggested pituitary stimulation or possibly its hypothalamic regulation, and Rabin[2] more specifically states that its action upon the hypothalamus causes the release of luteinising hormone releasing factor (LHRF), which acts on the anterior pituitary gland, thus releasing both follicle stimulating hormone (FSH) and luteinising hormone (LH). Clomiphene thus induces a rise in FSH which causes follicle growth. The second effect, a rise in LH, causes these follicles to secrete oestrogen. Unless these two reactions occur normally, there is no oestrogen surge, which in turn induces the pre-ovulatory LH rise. Under abnormal conditions, if the hypothalamic LH centre is suppressed, the oestrogen rise can occur with no LH surge or too poor an LH surge to induce ovulation.

The suggestive changes in oestrogen metabolism and the evidence of oestrogen antagonism indicate the possibility that clomiphene may have an additional site of action on the ovary, uterus or other peripheral site.

When administered to women with adequate endogenous oestrogen and an intact pituitary, clomiphene is followed by presumptive signs of ovulation. Further evidence of ovarian stimulation is afforded by ovarian enlargement, which is particularly associated with longer courses and higher doses.

Kistner[3] has pointed out that the precise dose of clomiphene citrate cannot be given since it will depend upon the type of patient being treated and upon the sensitivity of the ovary.

Since clomiphene is a potentially dangerous drug and because of documentation that 100 mg of clomiphene was sufficient to correct a malfunctioning sclerocystic ovary without the necessity of wedge resection of the ovaries, we have been using this low dosage of clomiphene on the fifth day of the menstrual cycle in selected patients, instead of the usually advocated dosage regimen of 50-100 mg for 5 consecutive days. The initial regimen was slowly increased according to the dosage schedule outlined below, until an adequate response was shown on the basal body temperature chart or until the patient conceived.

Our first patient on this low dosage was a 26-year-old woman who had been married for 5 years and had been trying for 4 years to become pregnant. The couple had been thoroughly investigated, and bilateral wedge resection of the ovaries had been performed 3 years previously for sclerocystic ovaries. Her previously grossly irregular menses had become regular and endometrial biopsies had repeatedly indicated ovulation. However, despite a normal seminal analysis, normal postcoital test and bilateral tubal patency, she had failed to conceive. Examination of her basal body temperature chart showed a biphasic response, but with an ill-sustained rise in temperature in the second half of the cycle. Treatment with thyroid, cyclical oestrogen and progesterone, and progesterone alone, had failed to achieve pregnancy. She was given 100 mg of clomiphene on day 5 of her cycle and became pregnant that month.

Encouraged by this initial success, we instituted this low dosage regimen of clomiphene in 89 selected cases, and 60 of these women became pregnant. It is the purpose of this article to present these successful cases.

SELECTION OF PATIENTS

The initial approach is entirely clinical and avoids the use of expensive laboratory investigations. It includes the history and an examination; a postcoital test and, if necessary, seminal analysis; endometrial biopsy on the first day of bleeding or full curettage in the premenstruum; and hysterosalpingography in the first half of the cycle or tubal insufflation at the time of curettage. A carefully and conscientiously recorded basal body temperature chart is kept for 3 months.

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The temperature chart is correlated with the endometrial histology, especially when the pathologist has reported a poor secretory phase. Where apparently normal ovulation is occurring, yet the patient is infertile, examination of the basal body temperature chart may show a shortening or lengthening of the ovulation-menstruation interval or an ill-sustained elevation of temperature.

If we exclude all other abnormal factors and deal only with defects in ovulation as the apparent cause of infertility, the 60 successful patients can be grouped and subdivided according to the endometrial histological pattern as follows:

Secondary amenorrhoea (5 cases)	
Inactive	2
Proliferative	2
Hyperplastic	1
Irregular cycles (41 cases)	
Anovulation	29
Defective ovulation	4
Apparently normal ovulation	8
Regular cycles (14 cases)	
Anovulation	5
Defective ovulation	6
Apparently normal ovulation	3

The patients thus fall into one of the following groups: anovulation—39 cases; defective ovulation—10 cases; apparently normal ovulation—11 cases.

Dosage Regimen

The dosage of clomiphene was determined by the response shown on the basal body temperature chart kept by the patients.

Scheme 1: The initial dosage instituted was 100 mg clomiphene on day 5 of a spontaneous or hormone-induced period. Where a clear-cut ovulation pattern was shown this dose was maintained for subsequent cycles. In certain instances clomiphene may result in the luteinisation of cystic follicles without ovulation, with subsequent secretion of progesterone from the luteinised cells. This will, of course, result in a sustained rise in the basal body temperature which might be mistaken for ovulation. Absolute evidence of ovulation is pregnancy. Careful recording of the basal body temperature chart is of paramount importance. In an amenorrhoeic patient included in this series, ovulation induced by 100 mg of clomiphene occurred on day 38 of the cycle. The patient was conscientious and kept a meticulous temperature record, thus enabling her to spot ovulation, and well-timed coitus resulted in pregnancy. Had she not conceived with this ovulation she would have received a higher dosage of clomiphene after the next period.

Scheme 2: If a response was not evident, then the next treatment cycle was increased by an additional 100 mg on day 6 of the cycle.

Scheme 3: 50 mg of clomiphene was given for 5 consecutive days, that is 250 mg per treatment cycle.

Scheme 4: 100 mg on days 5, 6 and 7, that is 300 mg per treatment cycle.

Scheme 5: The maximum dosage reached in patients in this series, if no response was obtained with the regimens outlined above, was 100 mg of clomiphene for 5 consecutive days, that is 500 mg per treatment cycle.

RESULTS

Sixty women fell pregnant after treatment with clomiphene. Their average age was 26½ years (range 20 - 38 years). The average duration of infertility at the time of the first consultation was 38 months (range 4 - 108 months). Fifty-one of the women suffered from primary infertility and 7 from secondary infertility. The average duration of the investigation before institution of clomiphene therapy was 4 months, and the average consultation-to-pregnancy interval was 5½ months (range 4 - 24 months).

Dosage Regimens Resulting in Pregnancy

Scheme 1 (100 mg): A total of 46 pregnancies resulted—37 after the first cycle, 2 after the second cycle, 5 after the third cycle, and 2 after the fourth cycle.

Scheme 2 (200 mg): A total of 14 pregnancies resulted —11 after the first cycle and 3 after the second cycle.

Scheme 3 (250 mg): Three pregnancies occurred after the first treatment cycle.

Scheme 4 (300 mg): Four pregnancies resulted after one treatment cycle.

Scheme 5 (500 mg): Three pregnancies occurred after the first treatment cycle.

Outcome of Clomiphene-Induced Pregnancies

A total of 70 pregnancies resulted from clomiphene therapy (10 women required clomiphene to become pregnant a second time). There were 44 live births (one set of twins), 9 abortions and 2 ectopic pregnancies, while 16 women are over 28 weeks pregnant and awaiting delivery.

Eight women conceived without further therapy after clomiphene-induced pregnancies.

Twenty-nine cases in this series were labelled 'clomiphene failures' when dosage scheme 5 did not result in pregnancy after 3 months. Pregnancy resulted in some of these cases some months after cessation of clomiphene therapy. The relationship of these treatments to these conceptions is not established and therefore not conclusive.

DISCUSSION

By definition, a couple are only considered to be infertile if there has been failure to conceive after trying for 2 years. This seems unrealistic and we think that the majority of gynaecologists would not hesitate to proceed with the investigation of a couple who have been trying for 6 - 9 months.

Clomiphene is the drug of choice in patients with cystic glandular hyperplasia whose problem is infertility. For those with polycystic ovaries, clomiphene is at least as effective as wedge resection, and may be required

where surgery has failed. However, when clomiphene has failed, surgery often succeeds.

It is also the drug of choice in those women who ovulate only two or three times a year, and because of this infrequency are infertile, and it is also correct initial treatment for patients with anovulatory menstruation of unknown aetiology.

Some apparently normal women with normal ovulation may in fact have abnormal corpus luteum function. Some of these patients may eventually become pregnant without treatment, but there can be no harm in giving these patients a small dose of clomiphene to help achieve an earlier pregnancy. Swyer[4] states that hyperstimulation with clomiphene is rare, even when a daily dose of 50-200 mg is given for 5 days. He recommends the use of short courses of clomiphene (for example 50 mg daily for 3 days from day 3 of the cycle) in women with ovulatory but irregular cycles, in order to reduce cycle variance and thus make the probable time of ovulation more predictable.

The cost of treatment with human gonadotrophins is high and careful monitoring with numerous hormone assays is necessary. There is also the danger of overstimulation, resulting in a high incidence of multiple births and, more serious, in the development of the 'hyperstimulation syndrome'. There is a very small range between a dose that will fail to stimulate follicular ripening at all and one which produces ovarian enlargement or multiple pregnancies. In contrast, our suggested regimen of clomiphene therapy is inexpensive and safe, and does not require laboratory investigations or careful monitoring.

It is of interest that there was only one set of twins in this series, whereas Shearman[5] reported 16% in his series (the dosage he used was 150 mg daily for 5 days). Kistner,[3] on the other hand, reported an incidence of only 8%. The increased incidence of multiple pregnancies is undoubtedly due to fraternal twinning, consistent with the observation of superovulation after clomiphene therapy. The low incidence in our series is undoubtedly due to the low dosage of clomiphene used.

Murray and Osmond-Clarke[6] reported that their patients, having conceived after clomiphene therapy, returned to their pretreatment menstrual patterns and required further treatment with clomiphene if they desired another pregnancy. This occurred in 10 patients in our series. However, 8 patients conceived a second time without further clomiphene therapy.

Some patients ovulated and conceived after cessation of therapy and were excluded from this series. Riley and Evans[7] and Osmond-Clarke *et al.*[8] reported that more than 50% of patients will have one to three subsequent ovulatory cycles at about 28-day intervals after cessation of clomiphene and that conception can occur before they return to their pretreatment irregularity. Murray and Osmond-Clarke[6] reported 32 pregnancies in subsequent cycles, and for this reason did not recommend repeated consecutive courses of clomiphene.

Our experience of a much higher pregnancy rate in the first ovulatory cycle is in agreement with that of other workers[9-11] and suggests that there may be a cumulative anti-oestrogenic effect of clomiphene, particularly on the cervical mucus. This would favour the rationale of intermittent rather than consecutive courses of clomiphene. Although MacGregor *et al.*[12] reported that in 8 999 treatment cycles the ovulation and pregnancy rate was virtually the same, irrespective of whether 50 mg or 100 mg of clomiphene were used, we would suggest that the smallest effective dose may improve results by reducing the anti-oestrogenic effect.

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