INCREMENTAL DOSES OF CLOMIPHENE CITRATE IN HYPOTHALAMIC ANOVULATION

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SUMMARY

483 cases of hypothalamic anovulation were induced with incremental doses of clomiphene citrate (CC). It was found that ovulation rates could be pushed up from 70.6% to 91.5% and conception rates from 48.9% to 73.9% in this way. Incremental doses of CC are therefore suggested before launching HMG or other similar therapies in patients branded as CC failures.

INTRODUCTION

Clomiphene citrate (CC) continues to be master drug in treatment of anovulation. However, improving pregnancy rates with this drug remains a challenge. Many workers (Hamond L. 1976, L. Charo et al, 1975) have shown that failure to achieve pregnancy with CC could be due to low doses of the drug. It is also interesting to note that low doses could also be responsible for failure to achieve a pregnancy even if ovulation may start occurring. It is due to these observations that different dosage schedules of this drug have been suggested (Garcia Flores et al 1984).

In the present prospective study of a decade, we are presenting our results with incremental doses of CC in hypothalamic anovulation.

MATERIALS AND METHODS

483 of our subjects who were treated for anovulation in unit III/I of the department of Obst. & Gynec., Medical College, Baroda are included in this study. The study period was of ten years commencing from 1st June 1986 to 31st May 1996.

Hypothalamic anovulation was labelled in those cases wherein no specific cause

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for anovulation could be determined after careful clinical and relevant laboratory investigations. We subjected all of these cases to our routine infertility workup. Anovulation was confirmed on ultrasonography. Postcoital test and assessment of tuboperitoneal status by laparoscopy was done. Hysterosalpingography was confined to those cases where a need to study the uterine cavity and tubal mucosal shadow was percieved. A routine semen analysis was also done. If there were other causes of infertility as well, their treatment of those causes was simultaneously started with ovulation induction.

CC was started in a dose of 50 mgms per day for five days from third day of the cycle. In cases of secondary amenorrhea, CC was similarly started after inducing a progestrone withdrawal. CC was given in this dose for 3 consecutive cycles or achievement of pregnancy whichever was earlier. Those cases which failed to achieve a conception within 3 cycles were divided into two separate groups. One group was of those subjects in whom ovulation occurred but there was no conception. The other group was of patients who remained anovulatory.

In both these groups, 100 mgms/day of CC was now started from the third day for five days. Once again this was for three months or achievement of pregnancy whichever was earlier. Those who failed to conceive were again divided into two groups as in 50 mgms of CC administration.

At this stage a break of three months was observed after which 150 mgms of CC/day was similarly started. It was given for three months. Once again conception, failure to ovulation and failure to conceive were the three groups classified.

In those cases where ovulation was not achieved in the first cycle of CC 50 mgms/day, 5000 IU of HCG was given when the follicle on USG was more than 18 mm in size. Needless to stress that most of the cycles were monitored on USG only. In the early part of the study we did not have an access to USG. Cycles were monitored on BBT chart with HCG administration done if required, on the day of the fall in temperature just before the ovulatory rise. This practice was given up as soon as USG become accessible to us.

RESULTS

483 cases of hypothalamic anovulation were treated with incremental doses of CC in the study period of ten years.

Table I
CC 50 MGMS/DAY (N=483)

	No.	%
Ovulated	341	70.6
Conceived	236	48.9
Ovulated but		
Did not conceive	105	21.7
Remained anovulatory	142	29.4

As shown in this table, with 50 mgms/ day of CC for five days 70.6% cases started ovulation. Of the 341 who ovulated, 236 conceived. 29.4% remained ovulatory.

CC 100 mgms/day for five days was given to two groups of patients: those 142 who did not ovulate with CC 50 mgms/ day for five days and those 105 subjects who ovulated but did not conceive with 50 mgms/day dosage schedule.

As shown in Table II 74 of the 142 (52.1%) subjects who were anovulatory in the first dosage schedule of CC ovulated with this second dosage schedule of 100 mgms/day for five days. Of these 74, 23 (31.1%) concieved. Thus, 47.9% remained anovulatory with this dosage schedule as well.

142 subjects were such who ovulated with the first dosage schedule but did not conceive. Thdy were also given 100 mgms/ day of CC for five days. 47.% of these - i.e. 68 of the 142 concieved now.

Those 68 subjects who failed to ovulate even with this second dosage schedule were given CC 150 mgms/day for five days. This dosage was also given to those 114 patients who ovulated with the second dosage schedule but still did not conceive.

Table II
CC : 100 MGMS/DAY (N=247)

	No.	%
Anovulatory in I, now ovulated (n=142)	74	52.1
Anovulatory in I, now concieved	23	31.1
Ovulated in I, concieved now (n=142)	68	47.9

Table III
CC : 150 MGMS/DAY (N=182)

	No.	%
Anovulatory in II, now ovulated (n=68)	27	39.7
Anovulatory in II, now concieved	14	51.9
Ovulated in II, concieved now (n=114)	42	36.8

Table IV
AGGREGATE RESULTS

	No.	%
Remained anovulatory	41	8.5
Ovulated but no conception	85	17.6
Ovulated and conceived	357	73.9

As shown in Table III 27 of the 68 anovulatory subjects ovulated and 14 of these conceived bringing the ovulation rate to 39.7% and conception rate to 51.9%. Of the 114 subjects who had started ovulating but did not conceive, 42 (36.8%), conceived with the incremental dosage of CC.

As shown in Table IV thus with increasing disages of CC, at the end only 8.5% subjects remained anovulatory and 17.6% were those who ovulated but did not conceive. 357 subjects (48.9%) conceived following this incremental schedule. This is to be compared with 236 conceptions (73.9%) when CC was given in the dosage of 50 mgms/day for 5 days. Thus, in 121 more subjects (25%) conceptions were possible with incremental dosages CC.

DISCUSSION

CC of wisely and scientifically used is known to give very satisfying results in anovulatory subjects. The standard dose of 50 mgms/day for five days can acheive upto 80% ovulatory rates and upto 50% conception rates. (Atlay & Pennington 1971). Improving these figures becomes interesting. Many methods have been tried, one of them being administering CC for longer duration than five days. (Garacia Flores, 1984). In this study we have used incremental doses of CC and documented the quantum of success at each dosage schedule.

High rates of ovulation but not an equally high rate of conception with CC could be explained by the failure of these women to develop an adequately functioning corpus luteum (Kistner, 1975). This could be the reason of acheiving pregnancy in women who start ovulating with lower loses but conceived on incremental doses.

There is no distinct trend of conception rates on increasing the doses of CC. 48.9% conceived with CC 50 mgms/day, 31.1% with CC 100 mgms and 51.9% with CC 150 mgms/day amongst those who ovulated.

HMG has good ovulatory rates and fair number of pregnancies as shown by many workers (Hock M. et al 1970, Schhenter J.G. et al 1981 and Wang C.F. et al, 1980). However, this therapy is more costly and has higher side effects. Incremental doses of CC circumvents these disadvantages and offers a fair pregnancy rate with 73.9% conception rates acheivable. HMG therapy and others can be kept in reserve for those who fail after incremental doses of CC.

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