Clomiphene citrate in Asian women

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CLOMIPHENE CITRATE, sold under the trade name of "Clomid," has not been freely available in this part of the world for use in Asian women and this is a preliminary report on 11 cases out of which 7 pregnancies resulted up till the time of writing.

Due to its scarcity, it has only been given to the most deserving cases for the sole purpose of inducing ovulation for fertilisation. Careful evaluation of patients includes preliminary dilatation and curettage, tubal insufflation, hysterosalpingogram and seminal analysis to ensure that at least physically there is no bar to conception – except for failure to ovulate.

Failure to ovulate was considered conclusive if the endometrium showed no secretory phase in the second half of the menstrual cycle, no biphasic basal body temperature curve and an oestrogenic smear in the second half of the cycle. Presumptive evidences considered are irregular menstrual cycles and failure to conceive after the patient was given advice about coitus during the imaginary fertile period of approximately 14 days before the onset of the next expected period.

Unfortunately, it is at present not possible to arrange estimation of urinary excretion of pregnanediol, oestrone, oestradiol or oestriol. Such procedures would be prohibitively expensive for the management of private patients of which this series is made up. Therefore to provide a measure of control, the help of a cytologist was enlisted.

In the series of cases, where possible, vaginal smears were taken in the second half of the menstrual cycle prior to therapy. This forms a good baseline for comparison with subsequent smears taken at various intervals following "Clomid" therapy. Of the cases studied, anovulatory smear patterns were seen in cases with non-secretory endometrium. This was also consistent with the presence of a monophasic temperature chart. Subsequently, smears were taken in the first half of cycle prior to "Clomid" therapy and in the third week following therapy. Smears were labelled "positive" for evidence of ovulation or "negative" when the smear pattern showed no change in pattern from a proliferative type smear in the first half of the cycle to a secretary type smear as seen in the post-ovulatory period in the second half of the cycle.

The accepted criteria for evidence of ovulation are the changes produced by the influence of progesterone on vaginal epithelium. Progesterone stimulates the proliferation and maturation of squamous epithelial cells as far as the intermediate cell stage. The characteristic "progesterone effect", seen in squamous cells obtained during the secretory phase,

consists of the curling of the cytoplasm of the cells resulting in the typical "rolled edge" appearance. The thinner cytoplasm of the more superficial squamous cells are folded back to give the "envelope effect". The cytoplasm attains a translucent granular appearance with a progressive increase in the number of cyanophilic cells which tend to aggregate in clumps. There is also progressive increase in neutrophils and histiocytes until just before menstruation, and with the proliferation of bacteria and fragmentation of cells, a late secretory phase smear gives a "dirty" appearance to the smear.

The initial dose is one 50 mg tablet, taken daily for 5 days, beginning on the fifth day of the cycle. Should ovulation occur, this dosage is maintained; otherwise, the dosage will be pushed up to 100 mg. daily and in a few cases 150 mg. daily were tried. To ensure a good seminal volume and count, the couples are advised to refrain from coitus until the 13th day of the cycles. It is believed that Clomiphene Citrate acts through the pituitary, causing an increased output of gonadotrophin, which stimulates the ovaries to develope and maturate its follicles. Overstimulation is minimised by careful adjustments of dosage as outlined above and pelvic examinations done before treatment and at the time of taking the second smear in the third week. Any ovarian enlargement has been treated with care and the patients were asked to report any acute lower abdominal pain which may indicate the rupture of multiple matured follicles.

Up to date, no serious untoward symptoms like nausea, hot flushes, blurring of visions and a host of others reported by European users, have been noted and this may be due to the small doses and short courses used in this series.

The following are summaries of the successful cases:-

(1) Mrs. V., Indian national, age 28. She is extremely obese, weighing 170 lbs. and is married 7 years with one abortion at 2½ months, occuring 5 months after marriage. She has, thereafter, consulted various gynaecologists in India and Singapore. Investigations completed by 24.6.68. The endometrium was non-secretory and showed cystic hyperplasia. Clomid was started on 14.10.68. She then consistently had Mittleschmerz (smear positive) and following L.M.P. on 2.6.69, complained of nausea on 12.7.69. Pregnancy test was positive but on 14.7.69, she began to stain and despite hospitalisation and hydroxyprogesterone caproate injections the pregnancy test became negative on 9.8.69 and products of conception was evacuated at D & C.

However, she reported amenorrhoea again following the next period on 17.8.69 and as a prophylaxis, weekly hydroxyprogesterone caproate was given. She is now 24 weeks pregnant. Foetal movement is felt and foetal heart heard.

(2) Mrs. V. P., Indian girl, age 26 and married 4 years. Normal girl who was first seen before marriage on account of oligomenorrhoea. One-and-a-half years following marriage, she was investigated for infertility and by 25.4.67, it was established she was anovulatory but nothing could be done. Her cycles continued to vary from 3 weeks to 4 months. Clomid was first started on 25.6.69 – that is, 27 months later, and by the fourth course, using 3 tablets daily, she ovulated and registered her L.M.P. on 18.10.69. Pregnancy tests done here and by an independent laboratory are positive and the uterus is now 14 weeks in size.

(3) Mrs. W. C. Y. Chinese, age 30. Normal girl, married 4 years. Usual treatment and most investigations completed by other gynaecologists except for hysterosalpinogram which was done on 6.1.69. Clomid started on 14.1.69 and she responded to the 2 tablets regime. Reported L.M.P. on 28.4.69 and except for morning sickness, pregnancy was progressing normally until 16.12.69 when the breech was found presenting. Attempt at external ecphalic version resulted in mild vaginal staining which settled after 5 days of hospital rest. She was delivered of a healthy 5 lb. 9 oz. boy by L.S.C.S. on account of disproportion.

(4) Mrs. P. T. French girl (an exception) married to a Chinese. Age 23 and married 3 years. She has a good growth of hair along the linea alba and is a thin, tall girl. Routine investigations completed by 8.11.68 were all normal except for non-secretory enometrium and a flat temperature chart throughout menstrual cycle. Patient refused Clomid therapy till 19.6.69 She responded to the first course and got pregnant after the second at the same dosage. Her L.M.P. was on 19.7.69 (smear positive). She had a short admission for severe hyperemesis gravidarum but is doing well now with the uterus at 28 weeks size. Foetal movement felt and foetal heart heard.

(5) Mrs. S. N. Chinese. Age 24 and married 2½ years with no issue. Investigations completed by 12.6.68 with non-secretory endometrium and a flat basal temperature chart. She responded well on the first course and in October 1968 became pregnant after the second (smear positive). She went on to have an uncomplicated pregnancy and was delivered by mid forceps of a normal 6 lb. 11 oz. baby girl.

(6) Mrs. L. K. L. Chinese. Age 22 and married 2½ years. Her problem was anovulation again – the investigation was completed on 22.7.68. She was started on Clomid on 16.10.68 and responded to the first course and was pregnant on the third (smear positive). Her pregnancy progressed smoothly and she delivered a normal 6 lb. 10 oz. baby girl on 12.9.69.

(7) Mrs. N. C. H. 28-year-old Chinese girl, married 6 years. She had one delivery 5 years ago. Despite no family planning, she was unable to conceive again. Investigations were completed by 25.4.69. After three months, there was no result and therefore on 22.7.69, she started on Clomid. She responded immediately and reported L.M.P. on 20.11.69. She is now 10 weeks pregnant and having mild morning sickness. Pregnancy test is positive and uterine enlargement present;

Of the remaining 4 cases, one case is of secondary infertility of 13 years' duration and she has had 4 courses with no evidence of ovulation having taken place. Two are married for 4 years and they, too, have taken 4 and 3 courses respectively. No result up to date. The last patient is married for one year and there has been no response after 2 courses.

Conclusion

This drug has been in use only recently and has shown very encouraging results in cases where it can be proved that failure to ovulate is the factor responsible for infertility. Perhaps the surprising fact is the one of secondary infertility who has failed to respond as she is the sort of patient deemed very suitable for treatment by Human Chorionic Gonadotrophin.

Three single pregnancies and none to suggest multiple ones show that simple clinical methods and cytology prove more than adequate in controlling patients put on this drug. It is indeed gratifying for both patients and doctors that so many patients have responded favourably and the fear of multiple pregnancies has not materialised. The cytologist report has not only added confidence when increasing dosage of the drug but it also saved wastage notwithstanding the fact that the drug at present is hard to come by and cost private patients a good deal of money.