SESSION 3

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Clomiphene therapy

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THE history of this compound, which is a triaryl-ethylene compound chemically related to trianisyl-chloro-ethylene (TACE) which is a weak oestrogen, is really rather remarkable because it was originally found to inhibit secretion of gonadotrophin and was blastotoxic in rats and therefore it was thought that it might prove to be a very efficient new oral contraceptive and was handed out to three groups of American workers, Kistner, Greenblatt & Tyler in 1960 and 1961, and they each came back independently with reports, that far from being an oral contraceptive it did in fact induce ovulation in women who were anovulatory and it was then submitted to a very prolonged and careful clinical trial before being finally released on the market.

Action of clomiphene

It stimulates in one way or another the ovaries to produce oestrogen. Indeed with the administration of clomiphene the urinary oestrogen level may rise to quite alarming heights; possibly it converts C₁₉ to C₁₈ compounds (androgens to oestrogens), but at the periphery it is anti-oestrogenic. For instance, it converts the oestrogenic vaginal smear into a smear which is not atrophic but which is rather similar in appearance to the smear produced when androgens have been administered. About 15% of patients complain of hot flushes while they are taking clomiphene which suggests that it acts clinically in an anti-oestrogenic way.

Various electro-encephalographic studies have been done with patients with anovulatory infertility and those who showed an abnormal EEG before the clomiphene was administered, whereas it became normal during administration, showed an 89% ovulation rate and a 53% pregnancy rate. Those who were abnormal before the clomiphene was given and remained abnormal after the clomiphene, showed an ovulation rate of only 45% and a pregnancy rate of only 10% while those who had normal EEGs before clomiphene and the EEG remained normal

while clomiphene was being given, showed a 45% ovulation rate and a 19% pregnancy rate. So, it appears that in some patients with an abnormal EEG, clomiphene converts it to a normal EEG and these patients respond appreciably better to clomiphene than other patients do, suggesting that it acts through the hypothalamus.

I think all we really are entitled to say about the compound at the present moment is that it apparently releases FSH and probably LH in the sort of ratio which enables ovulation to take place. This may be over-simplified, but at least it offers a possible explanation of how clomiphene may act.

Response to therapy

The response to clomiphene depends on the degree of ovarian failure. If the ovaries are already enlarged and possibly containing cystic follicles before clomiphene is given, these ovaries will be found to be extremely sensitive to the clomiphene and it is in these cases that over-stimulation effects may occur. For example, Southam & Janovsky (1962) produced massive stimulation of both ovaries and a pleural effusion and ascites when they were giving 100 mg daily for 14 days to one patient, but the ovaries were in fact double the normal size and round and very tense before they started the administration. However, 100 mg daily for 14 days in the days before manufacturers released clomiphene on to the market did not seem to be a very large dose. In the very early days of 1961-62 we quite often used 100 mg, perhaps 250 mg, daily for 14 days or longer and although we did sometimes over-stimulate the ovaries with such prolonged treatment and such large doses, amazingly this did not occur as often as one might now expect. Because of this factor of the sensitivity of the ovaries, Stein-Levental or polycystic ovaries, and cases of metropathia haemorrhagica with small follicles dotted all over the ovaries, tend to respond very much more rapidly and sensitively to clomiphene than, for

instance, so-called psychogenic amenorrhoea or amenorrhoea associated with galactorrhoea. The latter may of course have a different origin because the galactorrhoea may be due to secretion of prolactin at the expense of FSH and LH. In primary amenorrhoea the results are very poor indeed. In our own personal experience we have had no case of primary amenorrhoea respond to clomiphene. I think it is helpful to estimate the urinary gonadotrophins before embarking on clomiphene therapy because we have found that cases in which the urinary gonadotrophins were high, i.e. in the menopausal region, never gave any response at all. This presumably is because the ovaries were so resistant that they just would not respond to the clomiphene. On the other hand, no cases in which we were unable to detect any gonadotrophins in the urine at all, gave a response with clomiphene. It is quite obvious that if clomiphene acts by releasing gonadotrophins there must be some gonadotrophins there to be released and therefore it seems reasonable to try to find out before embarking on clomiphene about the state of affairs in regard to urinary gonadotrophin. So really when one comes to consider dosage it is very difficult to talk about a standard dosage. I think the dosage should depend on the degree of activity or deficiency of the ovaries. Obviously, where the ovary is chronically deficient and amenorrhoea has been present for months or years, those cases are going to respond less successfully to the standard minimal dose of clomiphene and it would seem quite reasonable to raise the dose of clomiphene certainly to 100 mg a day and possibly even to more than 100 mg/day. We had two standard courses before clomiphene came on the market. One was 100 mg daily for 14 days and the other was 200 mg daily for 4 days. It is obviously very safe and cautious to give 50 mg daily for 5 days which the manufacturers advise, but if there is no response to that dose I certainly think one should try 100 mg daily for 5 days before abandoning the treatment.

Control of therapy

If there are no other facilities available I think it is reasonable to monitor the treatment by such simple methods as basal temperature records, because one can at least see whether ovulation has taken place following the clomiphene or whether it has not. Uterine bleeding may occur some 2 or 3 weeks after finishing the course of clomiphene but quite often it is non-ovulatory bleeding. Basal temperature records will enable one to determine whether the bleeding is in fact ovulatory or not. A pelvic examination should certainly be carried out before the treatment with clomiphene is started, because if there is any suggestion that the ovaries

are already large and tender, clomiphene ought not to be administered. If there are facilities for doing serial vaginal smears while clomiphene is being given one can study the degree of oestrogenic response and, perhaps more important, the extent of the progestagenic response.

In those cases that responded to a course of clomiphene by ovulating, we found that about 50% had at least one more spontaneous ovulatory cycle after the initial dose of clomiphene, and therefore we do not give a second course of clomiphene in a month's time if we have had a response, but wait and see whether the patient produces her own spontaneous ovulatory cycle following on that, and furthermore we get the impression mainly from vaginal smear studies, that if one keeps on giving clomiphene month after month the patient responds less and less to the subsequent doses of clomiphene. When should one abandon treatment? Most patients of course are very averse to giving it up, but I feel that if the patient has not responded at all to three courses of clomiphene in adequate doses she is most unlikely to respond to further courses, and I certainly think that if the patient has not become pregnant after six courses of clomiphene she is extremely unlikely to become pregnant in the future.

In about 1964 we began to notice that some of the ovulatory cycles that we induced with clomiphene had a short luteal phase and that the degree of luteinization was not adequate for pregnancy to take place and we therefore started giving injections of chorionic gonadotrophin once ovulation had taken place, about twice a week for the next 2 weeks in doses of perhaps 5000, 3000, 2000 or 1500 IU, in order to strengthen the luteal phase of the cycle and to prolong it and I think some people now use HCG—human chorionic gonadotrophin—when they have got their maximal stimulation of the follicle with the clomiphene just to help ovulation to take place. Some people in fact give clomiphene and human pituitary gonadotrophin both at the same time, because they think that possibly the two together are slightly more effective than the one by itself. This habit of giving chorionic gonadotrophin with clomiphene has been reported on both by Kistner (1966) and by Jenkins & Ferriman (1969), as well as by our group at Chelsea.

Results

With regard to the results, Merrell have published in September 1970 a new brochure about clomiphene and they have reports on 5413 patients in the literature, or in cases reported to them; the overall ovulation has been 72.4%, and the pregnancy rate has been 30.6%. The pregnancy rate is calculated on all the cases and this includes some women who are not married and therefore not anxious to

have children and some women whose husbands are oligospermic. In our experience, if the pregnancy rate is confined to women who are anxious to conceive and in whom there is no other infertile factor, it is probably between 40 and 50%.

A number of double blind trials have been done on this preparation and in one, forty-one patients became pregnant on clomiphene and eight became pregnant on the placebo! One of course has always to remember when one is dealing with cases of subfertility that a successful outcome should often be attributed to the Almighty rather than to treatment given by one's own team!

The abortion rate is 25% which is high but then it is generally understood that women who have had difficulties about conceiving do have a high abortion rate.

Multiple pregnancies are liable to occur in about 10% and in our experience they have mostly been twins. I think we have had one set of triplets, but there have been reported three sets of quintuplets and even one set of sextuplets. There is no doubt that the multiple pregnancy rate is far less in the case of clomiphene than it is with gonadotrophins.

Minor congenital abnormalities such as hare-lip occur in less than 2% of cases.

The most frequently occurring side effects are hot flushes, but some patients complain of visual disturbances, flashes of light, blurring of vision and that sort of thing and if the clomiphene is discontinued the condition disappears. There is a tendency to bromsulphthalein retention in a certain number of cases and the manufacturers and Kistner (1966) both say that one should do liver function tests before administering clomiphene and that one should certainly not give clomiphene to women who have had liver disorders.

Conclusions

My final comment is that I think it is important

to remember that the only indication for giving clomiphene is to induce ovulation and that it is bad medicine to give clomiphene to women who are in fact already ovulating. You either induce ovulation or you do not induce ovulation. You cannot induce better ovulation. The sort of case I had sent to me from a doctor when clomiphene was not generally available was 'I hope you will be kind enough to give this patient, who is a very old friend of mine and a dear, sweet person whom I would like to help, a course of clomiphene. It is of course a pity that her husband is aspermic, but I think she would be very pleased if she had a course of clomiphene'.

It is of course true that with patients suffering from oligomenorrhoea, who may nevertheless ovulate 14 days before the next period does come on, this may be only about three times a year. Then I think it is reasonable to give clomiphene to try and increase the number of times they do ovulate during the year so that they will have a better chance of becoming pregnant.

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