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Chelsea Hospital for Women, London

Clinical Uses of Progestational Agents in the Endocrine Department of Chelsea Hospital for Women

F. Osmond-Clarke

Progestational agents are used in the treatment of women attending our clinic for the following reasons (Table I):

Table I

1. Premenstrual tension
2. Postponement of the menstrual cycle
3. Recurrent abortion
4. Menorrhagia – defined as *regular*, heavy *ovulatory* bleeding
5. Metropathia haemorrhagica – defined as *irregular*, heavy, prolonged, *non-ovulatory* bleeding
   a) Haemostasis
   b) Regulation of cyclical withdrawal bleeding
6. Infertility – associated with a short luteal phase

I will confine my remarks to the latter.

Infertility and short luteal phase

During the routine investigation of women with regular cycles, complaining of long standing infertility, serial vaginal smears and daily basal temperatures are used to pinpoint both the day of ovulation and the adequacy of the corpus luteum. Correlation of these methods with urinary pregnanediols, endometrial biopsies or laparotomy have made us confident of our assessment.

In our experience a luteal phase of 7–9 days duration is not an uncommon finding in women complaining of infertility, and as well as being of short duration the progestational effect on the vaginal epithelium is usually poor.

During our investigation of clomid for the induction of ovulation we were amazed at the incidence of induced ovulations which were followed by a short luteal phase lasting 6–9 days. This type of pattern recurred after each subsequent course of clomid.

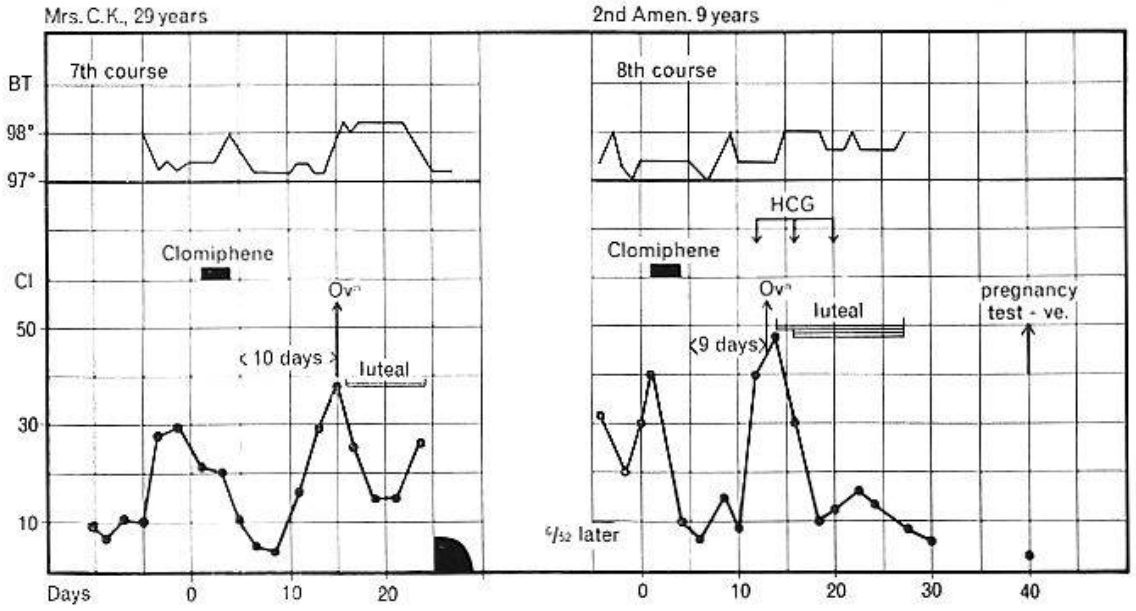

Fig. 1. Short luteal phase, treated with HCG.

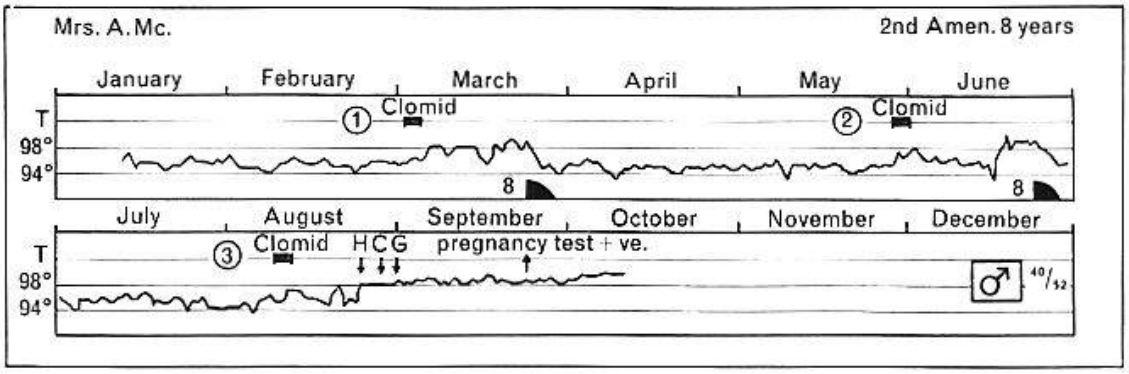

Fig. 2. Menstrual chart.

The apparent inadequacy of the corpus luteum both in women with regular infertile cycles and those following clomid-induced ovulations was treated by a progestational agent daily for 10 days following ovulation. Duphaston was our progestogen of choice. Very rarely conception occurred in the treated cycle. Some 4 years ago when reviewing the results of the first 200 women treated with clomid we found that the incidence of short luteal phases after induced ovulations occurred repeatedly in 25%.

Since our results with replacement therapy were so disappointing it seemed logical to try and improve the function of the corpus luteum by chorionic gonadotrophin. We treated $^2/_3$ of these patients and 50% conceived (Fig. 1). Combined clomid and chorionic gonadotrophin is now our routine procedure when there is evidence of an inadequate corpus luteum. The day of the initial injection of chorionic gonadotrophin is assessed cytologically and may be given just before ovulation or postovulation (Fig. 2).

However, when treating women with regular ovulatory cycles where the luteal phase is short, we prefer to give chorionic gonadotrophin in the immediate postovular phase, as when it is given preovulatory it may either have no apparent effect, upset the ovulatory rhythm, or even suppress ovulation in that cycle. This suggests that incorrect timing of the initial injection of chorionic gonadotrophin may in some patients upset their FSH/LH ratio.

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Discussion

A. Darragh: You said that you used clomid in seven courses. Are these consecutive courses or are they spaced? And what spacing?

O. Osmond-Clarke: We always space our courses of clomid, because we found in our first series of patients that 50% of the patients will have a further ovulatory period if you do not treat them at all. So, we always leave the patients if the first course is successful for six weeks to two months to make quite sure that there is no further spontaneous ovulation before further treatment is given.

A. Darragh: We have followed the same pattern of clomid and HCG, but I would make a slight difference. In our observations we obtained in the patients first of all a follicular phase response with a poor excretion of pregnanediol and no rise in plasma progesterone. Then, when we gave HCG on the 13th day of the clomiphene cycle, we found a luteal response with a rise in plasma progesterone and pregnanediol. So, while I would accept that you get a follicular phase with your clomid, I think that it is slightly inaccurate to call this also "ovulation". I do not think that ovulation occurred until you gave the HCG and I think perhaps you would have got the same result by giving just a single injection of 6000 units of HCG rather than three repeated doses.

O. Osmond-Clarke: Yes, I think you are quite right. I thought I said I do not really mind which day I give the chorionic gonadotrophins in the case of clomid. When there is evidence of a ripe follicle the chorionic gonadotrophin can be given to rupture the follicle and it can also be given after a spontaneous ovulation for its luteotrophic effect.

E. Diczfalusy: It is established now that the half-life time of circulating chorionic gonadotrophin in the human (Wide et al.: Acta endocr. [Kbh.] *59*, 579, 1968) is between 6 and 10 h, so that one would think that a single injection will be sufficient to induce ovulation.

O. Osmond-Clarke: I think it is, but there is evidence that the luteal phase can be improved by further injections of chorionic gonadotrophin.

B. Lunenfeld: After investigations some years ago on the clomiphene/HCG combination, we attempted to study this process and to try to find out which are the patients who need this kind of treatment. Because I think today we cannot just say "anovulation" or "amenorrhoea" or "primary amenorrhoea" or "primary amenorrhoea and galactorrhoea". We cannot use descriptive terms for a functional therapy. Now, when would we theoretically have to use a combination of clomiphene and HCG? I mean the first theoretic group which would need this would be a group which has a lack of release of FSH and lack of production of HCG or lack of release of FSH and only a small reserve in the production possibility of LH. Now this group is rather rare.

What may happen sometimes where the HCG will help is that you do get ovulations with a specific dose of clomiphene but the sensitivity of the target organ is low and by adding HCG after the ovulation has already occurred with clomiphene it will just bring about more luteinization of other follicles which have ripened during the clomiphene therapy in the ovary. This will thus strengthen our progestational effect in the uterus and help the nidation procedure. We find in our experiments that there is only a very, very small group who actually needs the clomiphene/HCG combination. Apparently we have found 2 cases of some 350 treatments which we have done which even need a combination of HMG/clomiphene. There again you have the opposite group in which you have got a lack of production of FSH and a lack of release but possible production of LH.

O. Osmond-Clarke: There is another type of response to clomid where the basal temperature does not indicate the true response. Following the typical clomid effect on the vaginal epithelium, there is a definite sustained follicular response without ovulation and the patient does not bleed.