

TRIPLET PREGNANCY IN A SUBFERTILE WOMAN TREATED WITH CLOMIPHENE CITRATE

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A 26-year-old subfertile woman with a history of abortions at the 7-9th week was treated with Clomid, 50 mg for 5 days. A pregnancy resulted, which ended in the premature birth of a set of alive triplets that sex and blood-group determinations showed to be trizygotic. It is suggested that this production of a multiple ovulation in a woman with luteal deficiency be the result of excessive dosage of Clomid.

In the treatment of sterility caused by lack of ovulation clomiphene citrate (Clomid) has been used for some years. Because of its easy handling, Clomid can in many cases be used in substitution for more complicated and costly treatments based on gonadotrophin of various origins.

Among the complications following the treatment based on HMG and above all on HPG, multiple pregnancies must be cited. Clomid is not exempt from drawbacks of this type, even though they are in a lower percentage as compared to gonadotrophin: 8-10% vs. 20-50% (Greenblatt et al. 1967, Johnson 1966). Most often, they are twin pregnancies, but cases of triple and quadruple pregnancies have occurred owing to superovulation with multizygotic fertilization (Naville et al. 1964, Bek et al. 1966, Kempers et al. 1967, Goldfarb et al. 1969).

The method of action of clomiphene is not yet completely clear; whatever the process may be, its administration causes an increase in endogenous gonadotrophin (FSH and LH) measured in the plasma. During and after clomiphene treatment, there is the so-called "clomiphene peak" of FSH and LH. It is thought that clomiphene acts either directly on the pituitary gland or through a hypothalamic-pituitary relay (Rabau 1967, Sharf et al. 1969).

The case that came to my attention seems to be worthy of mention because it lends itself to some clinical and therapeutic considerations.

It involved a woman of 26, married for 4 years, with regular menses, who, after 2 aborted pregnancies respectively at the 7th and 9th week, had been sterile for 2 years. Tests carried out on the patient had brought to light a slight uterine hypoplasia and deficient functionality of the corpus luteum; this emerged from histological and hormonal examinations carried out in the first and second half of the cycle, from the aspect of the basal temperature, and from the histological examination of the endometrium made on the 23rd day of the cycle.

After the first attempt of therapy with Clomid (50 mg for 5 days) the woman became pregnant. The pregnancy followed a normal course, although there was a considerable discrepancy between the volume of the uterus and gestational period, until the 30th week when an onset of labour led to hospitalization at the General Hospital of Ceprano where the diagnosis of a triple pregnancy was made after an x-ray.

Despite the therapy undertaken to prolong the pregnancy, delivery took place in the 32nd week. The infants, two male and one female, were alive and healthy and weighed respectively 1800, 1650, and 1400 g. The placenta was of the trichorial type and there were three amniotic sacs.

Examinations carried out on the infants' blood (the 1st male: O M rh₁Rh₂; the 2nd male: 0 MN Rh₂Rh; the female: 0 M Rh₂Rh) showed that they were trizygotic.

More detailed reports and those richer in case histories on pregnancies after Clomid treatment have not taken into account the incidence of multiple pregnancies in conditions of subfertility with deficient corpus luteum. I am not aware that this incidence has ever been taken into account by those who have studied the effects of gonadotrophin.

An explanation may be searched for in the fact that the fundamental indication for these therapeutic treatments (Clomid and gonadotrophin of human origin) has been represented by sterility of the non-ovulation type, i.e., of those sterilities characterized either by menstruation not preceded by ovulation, or by sporadic ovulation, or by primary and secondary amenorrhoea.

The majority of authors do not admit, however, that there is any ratio between the dose of Clomid and multiple pregnancies. As proof of that, they refer to the case of Cession and Gregoire (1969) of a woman who had been suffering from amenorrhoea for 17 months and gave birth to quadruplets after the second cycle of Clomid, 50 mg for 5 days.

In my case, however, the fact of having provoked several ovulations in a patient with a relatively good pituitary function but with insufficient functionality of the corpus luteum (owing presumably to a deficiency in luteinizing hormone releasing-factor and therefore of LH hormone) leads one to think that the dose of Clomid was excessive and that it would be better to keep traditional doses (50 mg for 5 days) for sterile women with no ovulation or oligovulation.

REFERENCES

- Beck P., Grayzel E.F., Young I.S., Kupperman H.S. 1966. Induction of ovulation with clomiphene. Report of a study including comparison with intravenous estrogen and human chorionic gonadotrophin. *Obstet. Gynecol.*, 27: 54-64.
- Cession G., Gregoire L. 1969. Non-published observations referred by Cession G. 1971. L'induction de l'ovulation par le clomiphène. *Rev. Méd. Liege*, 26: 17-25.
- Greenblatt R.B., Mahesh V.B., Pico I.R. 1967. In C. Wood (ed.): 5th World Congr. Gynaecol. *Obstet.*, Sidney. London: Butterworths.
- Goldfarb A.F., Morales A., Rakoff A.E., Protos P. 1969. Critical review of 160 clomiphene-related pregnancies. *Obstet. Gynecol.*, 31: 342-345.
- Johnson J.O. 1966. In Westlin and N. Wiqvits (eds.): *Proc. 5th Congr. Fertil. Steril.*, Stockholm. Amsterdam: Excerpta Medica Foundation.
- Kempers E.R., Decker D.G., Lee R.A. 1967. Induction of ovulation with clomiphene acetate. *Obstet. Gynecol.*, 30: 699-705.
- Naville A.H., Kistner R.W., Wheatley R.E., Rock J. 1964. Induction of ovulation with clomiphene acetate. *Fertil. Steril.*, 15: 290-309.
- Rabau E., Serr D.M., Mashiach S., Insler V., Salomy M., Lunenfeld B. 1967. Current concepts in the treatment of anovulation. *Br. Med. J.*, 4: 446-449.
- Sharf M., Sharf B., Bental E., Kuzminsky T. 1969. The electroencephalogram in the investigation of anovulation and its treatment by clomiphene. *Lancet*, 1: 750-753.

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