

# REPORT ON A CASE OF SUCCESSFUL INDUCTION OF OVULATION WITH CLOMIPHENE CITRATE

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Clomiphene citrate has only been available at the gynaecological endocrine clinic, Groote Schuur Hospital, since the early part of 1965. The following is a case report of a successful pregnancy following induction of ovulation by means of this drug.

## CASE REPORT

Mrs. V.B., a White female, aged 29 years, gravida 0, para 0, presented on 3 June 1964 with a history of secondary amenorrhoea for 8 months and primary infertility for 3 years.

The menarche had occurred at the age of 12, and the cycle had been 10-14/30-120 days since that time. The flow had been normal with no associated abdominal pain. A wedge resection of the ovaries in 1963 restored the cycle to a 5-8/30-day one, for 7 months. Since then there has been complete amenorrhoea. Breast, pubic and axillary hair developed at the age of approximately 12 years.

*Past history.* A diagnostic premenstrual curettage in 1960 had shown endometrial hyperplasia, absence of secretory activity, and no tuberculous endometritis. In 1963 an endometrial biopsy showed the same findings as above, and wedge resection of the ovaries was performed in April 1963. The ovaries were  $1\frac{1}{2}$  times normal size, not typical in appearance of hyperthecosis ovarii. Histological examination showed multiple follicular cysts with some luteinization of the theca interna but not all the features of the Stein-Leventhal syndrome. The patient also had psoriasis treated with systemic cortisone in 1961.

The family history showed no evidence of tuberculosis or diabetes. The patient's weight has been constant and there were no symptoms related to the thyroid or pan-

creatic glands. She was happily married and no psychological factors seemed to be present.

On examination she had a normally developed female appearance with all secondary sex characteristics present. There was no evidence of obesity or hirsutism. Systematic examination showed no abnormality.

Pelvic examination showed a normally developed vulva and clitoris. The uterus was normal in size and position. The ovaries could not be palpated and the cervix was healthy.

*Special investigations.* Cytology was normal and the cornification index was 6%. Progesterone withdrawal test—norethisterone 5 mg. *t.d.s.* for 10 days followed 14 days later by 5-day bleed. For endometrial and ovarian histology see past history.

Pituitary gland examination showed fundi and visual fields to be normal; X-ray of pituitary fossa was normal; FSH was 6 m.u. Adrenals—the 17-ketosteroids were 14.0 mg./24 hrs. and the 17-hydroxycorticosteroids 9.2 mg./24 hrs. Thyroid function—serum cholesterol 223 mg./100 ml.;  $^{131}\text{I}$  uptake, 51% of dose in 24 hrs., and RBC uptake, 16.8% of dose in 24 hrs., were both normal. Pancreatic function—the urine contained no glucose, and the GTT was normal.

X-ray of the chest was normal.

Blood investigations—haemoglobin 13.3 G./100 ml.; PCV 40%; MCHC 33%; WBC 4,120/cu.mm. The liver-function test was normal.

Infertility tests—both seminal analysis and hysterosalpingogram was normal.

*Conclusion.* It would appear that failure to ovulate was due to a primary pituitary gonadotrophic failure. Follicular function is present (oestrogen).

## TREATMENT

Pergonal (FSH from postmenopausal human urine), 500 mg./day intramuscularly for 10 days, followed by Pregnyl

(human chorionic gonadotrophins containing mainly LH and LTH), 6,000 units a day for 4 days, were given, commencing on 15 January 1965.

On this regime the CI rose from 6% to a maximum of 58%, 12 days after commencing treatment. Ferning of the cervical mucus which was present at day 10, gradually disappeared after day 18, and there was a rise in basal body temperature on day 12 which was maintained until she had a 5-day period, 26 days following commencement of therapy. Because of limited supplies of Pergonal it was decided to change therapy to Clomiphene.

Clomiphene citrate, 100 mg./day for 5 days, was commenced on 10 May 1965. On this treatment cornification rose from 4% to 9% on day 13; only slight ferning was present 2 days following the start of therapy and had disappeared by day 14; there was pain in the right iliac fossa on day 12 (? Mittelschmerz); a rise in basal body temperature occurred on day 14. The patient conceived during this cycle. She suffered no side-effects other than the above pain.

#### Progress of Pregnancy

*Antenatal.* No obvious hormonal insufficiency in early pregnancy as evidenced by low CI and absence of ferning. Failure of weight gain from 30 weeks gestation onwards—? slow growth of foetus.

*Labour.* Artificial rupture of membranes undertaken at 39 weeks because of loss of weight (2 lb.) from 38 to 39 weeks. Induction-delivery interval 5 hrs. Normal amount and colour of liquor and normal delivery.

*The puerperium* was uneventful. Normal lactation was well maintained. The infant was a female weighing 7 lb. 3 oz., and was normal. The placenta was macroscopically normal.

#### DISCUSSION

Clomiphene citrate is an analogue of the non-steroid oestrogen chlorotrianisene. The precise method of action is unknown. It may act directly on ovarian steroidogenesis.<sup>1</sup>

By acting on cytochrome C reductase in the ovary, this substance is reduced with resultant speeding up of the conversion of triphosphopyridine nucleotide (TPN) to its reduced state, dihydrophosphopyridine nucleotide (TPNH). The latter causes the aromatization reaction with increased secretion of oestradiol and oestrone. On the other hand its action may be primary at pituitary or hypothalamic level.<sup>2</sup>

It may compete with natural oestrogens for binding sites in the above organs, so displacing it and its inhibitory effects on these parts. A similar effect may operate at the peripheral sites, e.g. uterus.

#### Selection of Patients

(i) Anovulatory patients with adequate endogenous oestrogen secretion and normal thyroid and adrenal function. Results are much better in the presence of a proliferative—or, even better, hyperplastic—endometrium than when the endometrium is atrophic.

(ii) Normal or reduced pituitary gonadotrophins. However, Clomiphene will have no effect in the presence of complete pituitary failure.

(iii) Stein-Leventhal Syndrome.<sup>3</sup> Most of these patients will exhibit an ovulatory response to Clomiphene.

#### Dosage

The dose depends on the type of patient being treated, and the sensitivity of the ovary. Prior priming with oestrogen is not necessary. The initial dose is usually 50 mg./day for 3-5 days. If the ovaries are resistant, the dosage is increased but rarely exceeds 600 mg. per treatment cycle.

If withdrawal bleeding occurs, therapy is again commenced 10-14 days following the first day of the bleed. In the absence of any response, the second course is commenced after 30 days. At least 6 consecutive cycles of therapy should be given before concluding that the patient is a 'Clomiphene failure'.

#### Side-Effects

*Ovarian cysts.*<sup>4</sup> These are cystic follicles and cystic corpora lutea. Patients receiving Clomiphene should be watched constantly for the development of ovarian cysts. These usually regress spontaneously within 7-28 days.

The presence of an ovarian cyst before treatment contraindicates the use of the drug. In those patients who have had previous ovarian cystectomies, initial dosages must be very low. Hot flushes are not serious and disappear when therapy is discontinued.

Abdominal pain at the time of ovulation is common. Blurring of vision and spots of light have been noticed but no organic abnormalities have been found. Loss of hair is of a temporary nature and is never severe.

Clomiphene should not be used in the presence of pre-existing liver disease.

#### Results

Of a total of 1,731<sup>5</sup> patients treated for various indications, 70% had one or more ovulatory cycles. Ovulation occurred after the first course of treatment in 77%. In 16% ovulation only occurred after 2 or more courses. The best response (78%) was obtained in patients with the Stein-Leventhal syndrome. Pregnancy followed in 28% of those patients who ovulated.<sup>3</sup> However, many of these patients were single and others were not desirous of pregnancy.

Multiple pregnancy is more common ( $\pm 8\%$ ). This is similar to Gemzell's<sup>5</sup> findings in patients treated with human pituitary gonadotrophins.

There is no increase in congenital abnormalities.

#### SUMMARY

A case of anovulation successfully treated with Clomiphene is described. It is essential, firstly, to prove anovulation and then to make an extensive search for its many possible causes. Clomiphene will only benefit a small, selected group of patients.

I wish to thank Dr. C. J. T. Craig for his efforts in obtaining the drug, and the Wm. S. Merrell Company for making Clomiphene available to us. I should also like to thank Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, for permission to publish the case.

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