Successful induction of ovulation in normogonadotrophic clomiphene resistant anovulatory women by combined naltrexone and clomiphene citrate treatment

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Patients suffering from normogonadotrophic anovulation and infertility are initially treated with clomiphene citrate. Those who do not respond to clomiphene citrate usually receive gonadotrophin treatment which is labour-intensive, expensive, and associated with an increased risk of multiple pregnancies and ovarian hyperstimulation syndrome. We treated 22 patients with clomiphene resistant normogonadotrophic anovulation with naltrexone (an opioid receptor blocker) alone or naltrexone in combination with an anti-oestrogen. In 19 patients ovulation and resumption of a regular menstrual cycle was achieved and in 12 out of 19 a singleton pregnancy was observed. In conclusion, ovulation can be induced successfully using naltrexone alone or naltrexone in combination with an anti-oestrogen in clomiphene citrate resistant anovulatory patients. Compared to gonadotrophin induction of ovulation, this method is safe, simple and inexpensive.
Key words: endogenous opioids/naltrexone/normogonado-trophic ovarian failure/ovulation induction/polycystic ovary

Introduction

Anovulation and cycle abnormalities are associated with hypo-gonadotrophic hypogonadism [World Health Organization (WHO) group I], hypergonadotrophic hypogonadism, or normogonadotrophic status (WHO group II) (Rowe *et al.*, 1993). Most patients with anovulatory subfertility are normo-gonadotrophic with normal follicle stimulating hormone (FSH) concentrations, but luteinizing hormone (LH) concentrations are raised in some cases. The treatment of first choice is the use of anti-oestrogens, such as clomiphene citrate, during the early follicular phase. Eventually ~30% of normogonadotrophic anovulatory patients will prove to be clomiphene citrate resistant (Franks *et al.*, 1985).

Administration of human menopausal gonadotrophins (HMG) is recommended as the next approach for clomiphene citrate resistant anovulation (ESHRE Capri Workshop, 1995, 1996). This treatment provides an acceptable cumulative pregnancy rate but is expensive and potentially hazardous (Navot *et al.*, 1992). Treatments with low-dose step-up or step-down HMG or FSH have been developed to reduce the risk of hyperstimulation and multiple pregnancies, but they are labour-intensive (Buvat *et al.*, 1989; Hamilton-Fairley *et al.*, 1991; Fauser *et al.*, 1993)

Several groups have used naltrexone, an opioid receptor blocker, in patients with anovulation and cycle abnormalities. Endogenous opioids are among the factors involved in the inhibition of the hypothalamic pulse generator that directs gonadotrophin releasing hormone (GnRH) secretion. Nal-trexone establishes chronic blockade of the hypothalamic opioid receptors. Wildt *et al.* (1993a,b) reported that naltrexone treatment can restore ovulation and normal menstrual cycles in patients with various grades of hypothalamic ovarian failure. In contrast, Armeanu *et al.* (1992) and Couzinet *et al.* (1995) could not demonstrate an increase in gonadotrophin secretion or resumption of ovulation in women with hypogonadotrophic hypogonadism after naltrexone treatment. In a group of patients with weight-loss-related amenorrhoea, administration of nal-trexone resulted in the restoration of a normal menstrual cycle (Genazzani *et al.*, 1993). In women with polycystic ovarian syndrome LH concentrations were normalized after naltrexone treatment (Lanzone *et al.*, 1993; Cagnacci *et al.*, 1994).

We wished to investigate whether patients with subfertility due to normogonadotrophic anovulation, who were clomiphene citrate resistant, ovulated after oral treatment with naltrexone alone or naltrexone in combination with anti-oestrogens. Our goal was to keep the treatment as simple and efficient as possible and to avoid side-effects and complications.

Materials and methods

Subjects

We based our study on treatment cycles from January 1995 to September 1996 in 22 infertile women with amenorrhoea ($n = 11$) or oligomenorrhoea (fewer than six periods a year; $n = 11$). Thirteen patients suffered from primary subfertility and nine from secondary subfertility. Exclusion criteria were hyperprolactinaemia, thyroid hormone abnormalities, tubal damage (tested by hysterosalpingography or laparoscopy) and abnormal sperm count ($<20\times10^6$/ml). All patients were normogonadotrophic and previously received, in two cycles, clomiphene citrate (Serophene; Serono Benelux, Amsterdam, The Netherlands) in doses up to 150 mg for 5 days with no signs of ovulation on ultrasound, nor resumption of a regular cycle.

Treatment schedule

Naltrexone treatment was started on the first cycle day of a spontaneous or progestagen-induced menstrual cycle. Naltrexone (Nalorex; Dupont, Nemours, France) was administered orally in a dose of 25 mg twice daily. Regular visits were scheduled for ultrasonic cycle monitoring. Ultrasonograms were obtained using a 5 MHz vaginal

Table I. Patient characteristics and median (and range) baseline plasma concentrations in 22 normogonadotrophic anovulatory clomiphene citrate resistant women

Age (years)	29	(24–35)
Duration of subfertility (years)	2.4	(0.7–10.7)
Luteinizing hormone (IU/l)	9	(1–28)
Follicle stimulating hormone (IU/l)	5	(2–11)
Oestradiol (pmol/l)	219	(88–422)
Testosterone (nmol/l)	1.9	(0.6–5.5)

probe (Toshiba Medical Systems, Europe BV, Zoetermeer, The Netherlands) from cycle day 9 onwards. When a leading follicle (>10 mm diameter) was detected, ultrasonographic monitoring was performed every other day until ovulation had occurred. Progesterone concentrations were determined 1 week later. Progesterone was estimated in a commercially available heterogeneous competitive magnetic separation immunoassay (Bayer, Tarrytown, NY, USA). The total variation coefficient is between 2.8 and 13.8%).

If the patient did not respond to naltrexone alone, 100 mg of clomiphene citrate for 5 days was added to the continuous naltrexone therapy. If ovulation was demonstrated, the present treatment was continued using basal body temperature chart (BBT) instead of ultrasound detection of ovulation. Up to six cycles per patient were included in this study. Ovulation was considered to have taken place in the case of ultrasonographic signs of ovulation, and/or elevated midluteal progesterone (>30 nmol/l), and/or biphasic BBT, and/or resumption of a regular menstrual cycle and if pregnancy occurred. Naltrexone was discontinued in the case of a positive pregnancy test or when patients had no follicular growth after 21 days of combined naltrexone and clomiphene citrate treatment.

Hormone assays

Baseline hormone samples were drawn at day 1, 2, 3 or 4 of a spontaneous or progestagen-induced menstrual bleeding. All hormones were assayed by commercially available kits. Plasma LH and FSH concentrations were determined in a heterogeneous sandwich magnetic separation assay (Bayer, Tarrytown, NY, USA). For LH the inter- and intra-assay coefficient of variation was 4.5% and for FSH 3.2%. Oestradiol was determined using a commercially available radioimmunoassay (DPC, Los Angeles, CA, USA) with intra- and inter-assay coefficients of variation between 4.2 and 7.4%. Oestradiol concentrations <200 pmol/l were measured using a double antibody radioimmunoassay with a total variation coefficient 2.7%. Testosterone was assayed using coat-a-count radioimmunoassay (DPC) whose total variation coefficient was 12.9%.

Results

Patient characteristics are shown in Table I.

In 19 of 22 patients ovulation was achieved. Four patients ovulated on naltrexone alone, 18 patients needed clomiphene citrate. Twelve patients conceived during treatment. Three patients conceived in their first cycle, four in their second, two in their third, two in their fourth cycle and one in her fifth cycle. All pregnancies were singleton pregnancies. At the time of going to press, two spontaneous abortions have occurred and 10 pregnancies are ongoing.

Figure 1 shows the change in frequency of menstrual periods following naltrexone treatment. In those patients who conceived, the virtual cycle length of that cycle was estimated by extrapolating from the length of the follicular phase. Median
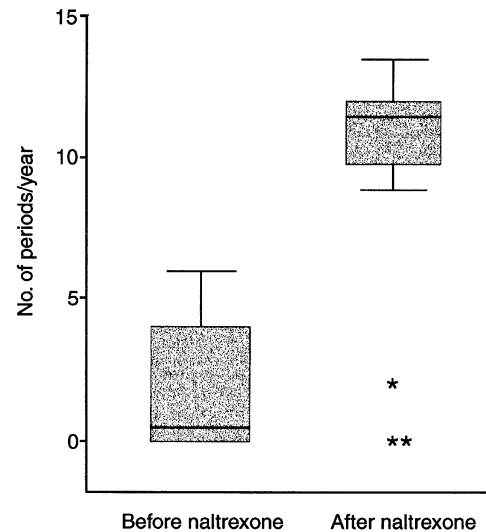
Figure 1. Number of menstrual periods in 22 anovulatory women before and after treatment with naltrexone. Boxes indicate the 25th and 75th percentile, with a solid line within the box showing the median value, whereas whiskers show the largest and smallest observed value that is not an outlier. Outliers are shown by asterisks in the plot and are defined as values more than three box-lengths from the 25th or 75th percentile. Data shown for women before naltrexone treatment include several amenorrhoeic patients, thus resulting in a menstrual frequency skewed towards zero, and the coincidence of the 25th percentile and lowest observed value.

frequency of menstrual periods per year changed from 0.5 (range 0–6) to 11.5 (range 0–13.5) after treatment. Three patients did not respond to combined therapy. Prior to treatment two of those patients had amenorrhoea and one patient was severely oligomenorrhoeic (two periods/year). All three had polycystic ovarian disease (PCOD).

Only minor side-effects were observed during drug administration. Some patients reported some discomfort (dizziness, anxiety, restlessness or malaise) during the first few days of naltrexone treatment. These symptoms usually disappeared spontaneously after several days.

Discussion

This is the first study which shows the successful induction of ovulation by combined administration of an opioid receptor blocking agent and an anti-oestrogen in normogonadotrophic clomiphene citrate resistant anovulatory women. Patients with normogonadotrophic anovulation who do not respond to treatment with clomiphene citrate are considered to be the most difficult group of patients to treat. Most have PCOD, and when they are treated with HMG their ovaries tend to hyperrespond. In order to avoid this complication, frequent monitoring is essential during HMG therapy, which is very time-consuming for both doctor and patient.

We found that 86% of our normogonadotrophic clomiphene citrate resistant patients responded to naltrexone or naltrexone and clomiphene citrate. Ovarian hyperstimulation syndrome and multiple pregnancies were avoided; in our study only monofollicular growth was observed and all pregnancies were singleton pregnancies. The oral administration of the drug is

simple. Our results suggest that, once ovulatory response is obtained, monitoring can be limited, thus making frequent visits unnecessary. The resumption of regular cycles proved to be consistent: the seven patients who ovulated but did not become pregnant showed no change in cycle duration during six cycles. In conclusion, our proposed treatment was simple and cost-effective.

There will never be a single solution to the cause of normogonadotrophic anovulation. All along the hypothalamic–pituitary–ovarian axis, factors may be responsible for cycle abnormalities. Clomiphene citrate is thought to displace endogenous oestrogen from hypothalamic oestrogen receptor sites, resulting in an alteration of GnRH secretion and eventually in an increased FSH production in the pituitary. Opioid antagonists may affect follicle development and ovulation by modulating the GnRH secretion and thus influencing major endocrine regulatory pathways. Apparently, some anovulatory, clomiphene resistant patients may respond favourably to inhibition of their endogenous opioids. This suggests that in these cases an opioid-dependent hypothalamic–pituitary dysfunction, possibly similar to the functional defect in hypogonadotrophic hypogonadism, is responsible for the abnormal cycle dynamics. In addition, patients who do not respond to either clomiphene or naltrexone alone may start ovulating during combination therapy. It seems that the mechanism of follicular selection and dominance remains operative or is restored, since only monofollicular development and singleton pregnancies were obtained. Naltrexone offers an effective, safe, simple and cheap alternative to gonadotrophin ovulation induction in clomiphene resistant patients with cycle disturbances.

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