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Combination of Clomiphene Citrate and Tamoxifen for Ovulation Induction

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Summary

Thirty six normoprolactinemic anovulatory infertile patients were taken for the study. These patients were randomly assigned to two groups. Patients in group A were treated with 50mg clomiphene citrate for three consecutive cycles and then with 50mg clomiphene citrate and 20mg tamoxifen for the next three subsequent cycles. While the patients in group B were treated with 50mg clomiphene citrate and 20mg tamoxifen for three consecutive cycles followed by 50mg clomiphene for the next three cycles. The effect of the treatment was monitored in the form of hormonal and endometrial response, ovulation rate and successful pregnancies. The study was designed as a prospective, randomized, cross over trial to eliminate any additional factors that could affect ovulation. The ovulation and pregnancy rates were higher with combination therapy but the results were not statistically significant. There was no pregnancy loss in this group while two patients had spontaneous abortion in clomiphene alone group. Therefore, carry home baby rate was significantly higher in combination group.

It may be concluded that, clomiphene and tamoxifen combination therapy holds much promise in the future in achieving not only high ovulations rates, but also higher pregnancy rates and term pregnancies in anovulatory infertile patients.

Introduction

Amongst the various causes of infertility, failure to ovulate is a major cause in approximately 40% of the cases in the females (Speroff et al, 1994). Discovery of ovulation inducing agents has been a therapeutic breakthrough in inducing ovulation and attaining pregnancy in these patients. Since long clomiphene has remained the first line of treatment for it. In the patients who were resistant to the standard therapy with clomiphene citrate ovulation was successfully induced by adding other hormonal agents.

Tamoxifen was a known antiestrogenic drug for quite a few years, used very frequently in the treatment of breast cancer. This drug is also an effective inducer of ovulation. It has been found to be effective in inducing ovulation even in women unresponsive to clomiphene citrate therapy. Tamoxifen is also known to treat luteal phase defect whereas, clomiphene can both cause and treat this problem. In addition to all these, unlike clomiphene, it has beneficial effect on the endometrium.

Thus came the next logical step of combining lower doses of clomiphene citrate with tamoxifen to achieve high ovulation rates as well as higher pregnancy rates. Williamson and Ellis (1973) were the first to use tamoxifen for induction of ovulation. Suginami et al (1993) used the combination therapy of clomiphene and tamoxifen to induce ovulation with good results. But this combination did not attain wide acceptance. The present study endeavors to test this combination in Indian population.

Materials and Methods

This was a prospective, randomized, cross over study to eliminate any additional factors that could affect

ovulation.

1. Selection of Patients
   Thirty six normoprolactinemic anovulatory infertile patients were taken for the study. These infertile patients had normal semen analysis, hysterosalpingography (HSG) and diagnostic laparoscopy findings, but were anovulatory. Hormonal profile was done in these patients on day 3 and day 5 of the cycle for FSH, LH, T3, T4, TSH, prolactin, estradiol and testosterone levels and in midluteal phase of the cycle for progesterone levels. Infertility was defined as inability to conceive after one year of unprotected intercourse. Anovulation was defined when mid luteal serum progesterone was less than 3ng/ml.
   These patients were randomly assigned to two groups, group A and group B. Patients in group A were treated with 50mg clomiphene citrate for three consecutive cycles and then with 50mg clomiphene citrate and 20mg tamoxifen for the next three subsequent cycles. While the patients in group B were treated with 50mg clomiphene citrate and 20mg tamoxifen for three consecutive cycles followed by 50mg clomiphene for the next three cycles. Clomiphene and tamoxifen were administered to the patients from day 5 to day 9 of the cycle in both the study groups.
2. Ovulation was documented (a) by midluteal serum progesterone level exceeding 7ng/ml. For this a single level of progesterone was done on day 23 of the cycle. (b) by ultrasound showing evidence of ovulation or (c) by pregnancy ensuing.
3. Serum estradiol levels were recorded on day 14 of the cycle by radioimmunoassay.
4. Endometrial thickness was noted by transvaginal ultrasonography (TVS).
5. Pregnancy was documented either with positive urine beta human chorionic gonadotrophin levels and/or ultrasonography.

Observations

Out of total 36 patients, 2 in group A were lost to follow up after 1st and 3rd cycles and 2 in group B were lost to follow up after 1st and 2nd cycles. There was no difference in clinical and hormonal profile of two study group (Table I). Ovulation rate was 72% per cycle in clomiphene group and 79 % in clomiphene and tamoxifen group. Pregnancy per treated cycle (Table II) was more in clomiphene / tamoxifen group but not significantly more. ($P < 0.05$). The two abortions occurred with the clomiphene alone group only. No pregnancy wastage occurred in the combination group. Though estrogen and progesterone response was higher in the combination group, it was not significantly so. There is no difference in maximum endometrial response (recorded by TVS) in two groups (Table III). No pregnancy was achieved if estrogen response was <200pg/ml. Most of viable pregnancies took place when progesterone was greater than 10ng/ml and the endometrial response was greater than 9mm.

Table I : Clinical background and hormonal milieu of the patients prior to initiation of the treatment.

Parameters	Group A N =18	Group B n=18
Age	24.38 ± 2.25 yrs	24.83 ± 2.52 yrs
Duration of infertility	3.56 ± 1.16 yrs	4.08 ± 2.40 yrs
Primary infertility	14	13
Secondary infertility	4	5
LH	3.06 ± 2.3 miu/ml	3.69 ± 2.57 miu/ml
FSH	4.54 ± 0.93 miu/ml	5.09 ± 1.41 miu/ml
Prolactin	17.32 ± 12.94ng/ml	13.27 ± 5.5ng/ml
Testosterone	49.99 ± 11.31ng/ml	48.19 ± 22ng/ml
Estrogen	56.033 ±25.96pg.ml	44.83 ± 16.4pg/ml
Progesterone	0.94 ± 0.61ng/ml	1.35 ± 0.81ng/ml

Table II – Ovulation and pregnancy achieved in the treated cycles

	Clomiphene	Clomiphene / Tamoxifen
Total no of cycle treated	79	78
Ovulation achieved	57 (72%)	62 (79%)
Pregnancy achieved	5 (6.3%)	7 (8.9%)
Abortion	2	0

Table – III Hormonal and endometrial response to drug therapy-

	Clomiphene	Clomiphene / Tamoxifen
Estradiol pg/ml 12th day of cycle	333.35 ± 220.13	403.507 ± 242.307
Progesterone ng/ml 23rd day of cycle	26.25 ± 25.71	30.58 ± 26.56
Maximum endometrial Response in mm	9.24 ± 1.29	9.3 ± 1.36

Discussion

Suginami et al (1993) achieved ovulation rate of 43.9% per cycle with clomiphene and 75% with clomiphene and tamoxifen. We obtained ovulation rate of 72% per cycle with clomiphene alone (57 cycle were ovulatory) and 79% per cycle with clomiphene and tamoxifen combination (62 cycle were ovulatory). Ovulation was more in the combination group but it was not of statistical significance.

In the patients treated with clomiphene alone, 5 pregnancies were achieved. Out of which one was a twin pregnancy and two pregnancies resulted in early pregnancy losses. Whereas, in patients treated with combination therapy seven pregnancies were achieved, all were singleton pregnancies and there was no pregnancy wastage in them. Therefore carry home baby rate was higher in clomiphene group 8% (3/36) in clomiphene alone group and 18% (7/36) in combination group. The difference is not statistically significant due to small number of patients. Better outcome can be attributed to the ability of tamoxifen to prevent and to treat luteal phase deficiency by lengthening the luteal phase (Fukashima et al 1982). In addition, the less pronounced deleterious effect of combination therapy on the endometrium and cervical mucus may also have a role to play (Annapurna et al 1997).

Various authors have shown that the estrogen and progesterone levels increase as a result of clomiphene and tamoxifen as compared to normal cycle. Senoir et al (1978) compared the effect of clomiphene and tamoxifen on plasma estradiol and progesterone levels. They showed that clomiphene therapy results in rise in the levels of both estradiol and progesterone. However concentrations attained were often much greater than those observed in normal menstrual cycle. Tamoxifen also, in a similar fashion, results in increase in the mean concentration of estradiol in the preovulatory period and in the luteal phase, relative to the values seen in the controls with normal cycle. The mean concentration of progesterone was also higher in the luteal phase with tamoxifen. An increase in the concentration of estradiol and an overall increase in the luteal phase progesterone concentration has also been reported by Tajima and Fukushina (1983). The increase in luteal activity following treatment with tamoxifen, probably reflects an increase in the size and secretary activity of the preovulatory follicles which leads to increased mass of luteal tissue for synthesis of progesterone. We compared the estrogen and progesterone response in the two treatment groups. As seen in table III, the rise in serum levels of estrogen and progesterone was higher in patients treated with combination therapy, though it was not statistically significant.

Hull et al (1982) in their paper, stated that, single serum progesterone level provides a clinically reliable criterion of potential fertility. In spontaneous cycle conception occurred when serum progesterone ranged from 8.5 to 16.7ng/ml the lower limit being 9.4ng/ml. Our results also showed that almost all pregnancies ensued when serum progesterone was greater than 10ng/ml. In two patients progesterone levels were less than 10ng/ml. These pregnancies ended in abortions.

Ultrasound observation of the endometrium has revealed that, successful implantation depends on adequate endometrial response. An antagonistic effect of clomiphene on endometrium based on histological studies has long been known (Sterzik et al, 1988). It is also known that tamoxifen gives rise to hyperplasia of the endometrium (Deligdisch, 1993). Ugur et al (1998) reported that, the combination treatment has less deleterious effect on the endometrium. Hence, we compared the endometrial response in the two treatment groups using transvaginal sonography. However, the difference between the two groups was not statistically significant.

To conclude we can say that clomiphene and tamoxifen combination therapy holds much promise in the future in achieving not only high ovulation rates, but also higher pregnancy rates and term pregnancies in anovulatory infertile patients

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