

Comparison of efficacy of Clomiphene Citrate and Tamoxifen for induction of Ovulation among women with Anovulatory Infertility

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Abstract

Background: Infertility is a global problem among the married couple. Globally 10 to 15 percent of the couples are experiencing this problem. Anovulation is one of the major causes of infertility. Clomiphene citrate and tamoxifen- both drugs are selective estrogen receptor modulators. In women with anovulatory infertility, both of these drugs have been used for induction of ovulation. This study compared the efficacy of these drugs for induction of ovulation, endometrial response and pregnancy rates.

Methods: A prospective, comparative study conducted in infertility clinic of Tribhuvan University, Kathmandu. Women who failed to develop dominant follicle for consecutive three cycles were considered as anovulatory. In 200 such women ovulation was induced with clomiphene (100 cases, group A) and tamoxifen (100 cases, group B). Selection of the women in these two groups was done blindly, picking up the envelope containing chit, written A or B. Dose of clomiphene ranged from 50-150 mg and that of tamoxifen 20-60mg. Follicular monitoring was done by transvaginal ultrasonogram from 9th day of the cycle. Development of follicle, endometrial response, ovulation rate and pregnancy rate recorded and analyzed.

Results: In group A women, endometrial thickness decreased with increase in the dose of drug, but in group B women, endometrial thickness increased with increase in the dose of tamoxifen. Ovulation occurred 63 % in group A and 61 % group B. Pregnancy rate was 17% among group A and 21% among group B.

Conclusion: Tamoxifen is an equally effective alternative for induction of ovulation.

Key words: clomiphene citrate, tamoxifen, ovulation induction.

Introduction

Ovulation is a core event for reproduction. Among the causes of infertility, 20-25 % accounts for anovulation [1]. Clomiphene citrate (cc) is most widely used drug for induction of ovulation. Pregnancy rate with clomiphene citrate is 30-40 %, but ovulation rate of 70-80% [2]. The disparity between ovulation and pregnancy rate may be due to antiestrogenic action of CC on endometrium and cervical mucus. Tamoxifen (TMX) is another drug similar in structure to clomiphene and is used for induction of ovulation with reported ovulation rate of 50-90% and pregnancy rate 30-50% [3,4,5]. The better ovulation and pregnancy rates with tamoxifen may be due to higher score on endometrium and cervical mucus and better functioning corpus luteum [3,6].

Materials and methods

This was a prospective, comparative study, done on two hundred women with anovulatory infertility attending infertility clinic of Tribhuvan University, Teaching Hospital Kathmandu. Duration of the study was two years from August 2007 to July 2009. History of all the couple with primary infertility was taken in detail. Couple were examined, counseled and investigated. Thyroid disorders, hyperprolactinemia, abnormal levels of follicle stimulating and luteinizing hormone levels were ruled out. Tubal patency test was done by hysterosalpingogram (HSG). Husband's semen analysis was done. Follicular monitoring was done by transvaginal sonogram (TVS) from 9th day of the menstrual cycle. Absence of development of dominant follicle (18-22

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mm) in three consecutive menstrual cycles by TVS was considered as anovulatory infertility. These women with anovulatory infertility were again counseled and written consent was taken from those who agreed to be enrolled in the study. Women with anovulatory infertility were divided in two groups. In women of Group A, ovulation was induced with clomiphene citrate, starting from 50mg to 150 mg/day from second day of cycle for 5 days. Clomiphene was given 50 mg/day in first cycle. If there was no adequate size follicular development the dose was increased in next cycle. Clomiphene was repeated maximum for 6 cycles. In Group B women, the ovulation induction was done with tamoxifen 20-60 mg /day from the same day of menstrual cycle and same duration as clomiphene.

Exclusion criteria

Women with bilateral tubal block, those husbands were oligo or azoospermic, women below 20 or above 40 years of age, anovulation class 3 (hypergonadotrophic-hypogonadism), women with active liver disease, diagnosed case of Asherman's syndrome, hyperprolactinemia, thyroid dysfunction, secondary infertility, diagnosed cases of myoma uteri, endometriosis, ovarian tumor, hydro- or pyosalpinx, pelvic tuberculosis, genital tract anomaly, history of chemo or radiotherapy, conization of the cervix, on antipsychotic, anti-hypertensive, antiemetic drugs or hormones.

As shown in figure 1 and 2 endometrial thickness was 8-13 mm in 91 percent patients when clomiphene was given 50 mg. With increase in dose, percentage of women with this thickness of endometrium decreased. In tamoxifen group, some of the women had endometrial thickness more than 14 mm with 40 and 60 mg of the drug.

Results

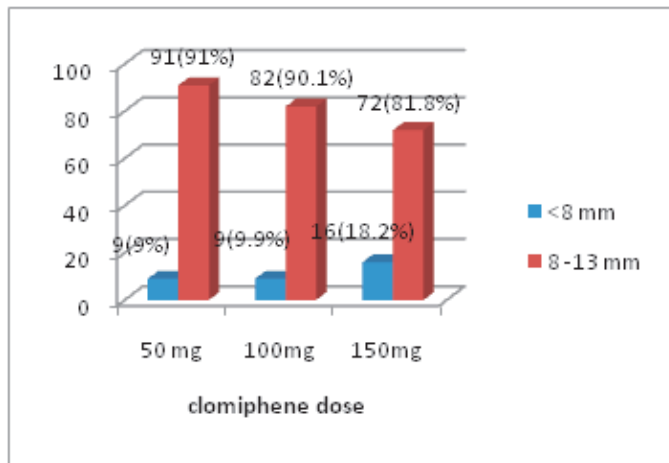


Figure 1

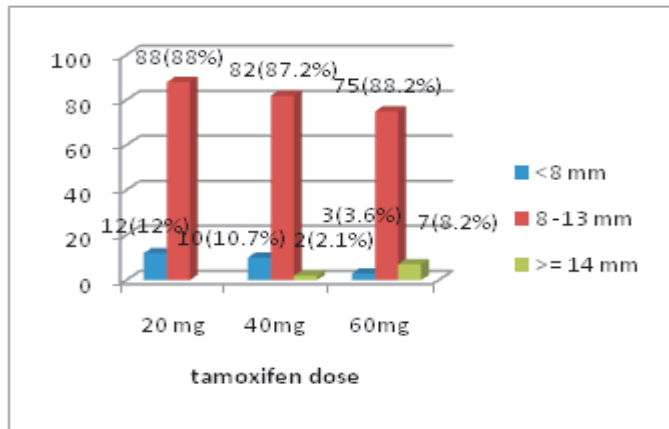


Figure 2

Figure 1 and 2. Response of endometrium to different doses of clomiphene citrate and tamoxifen

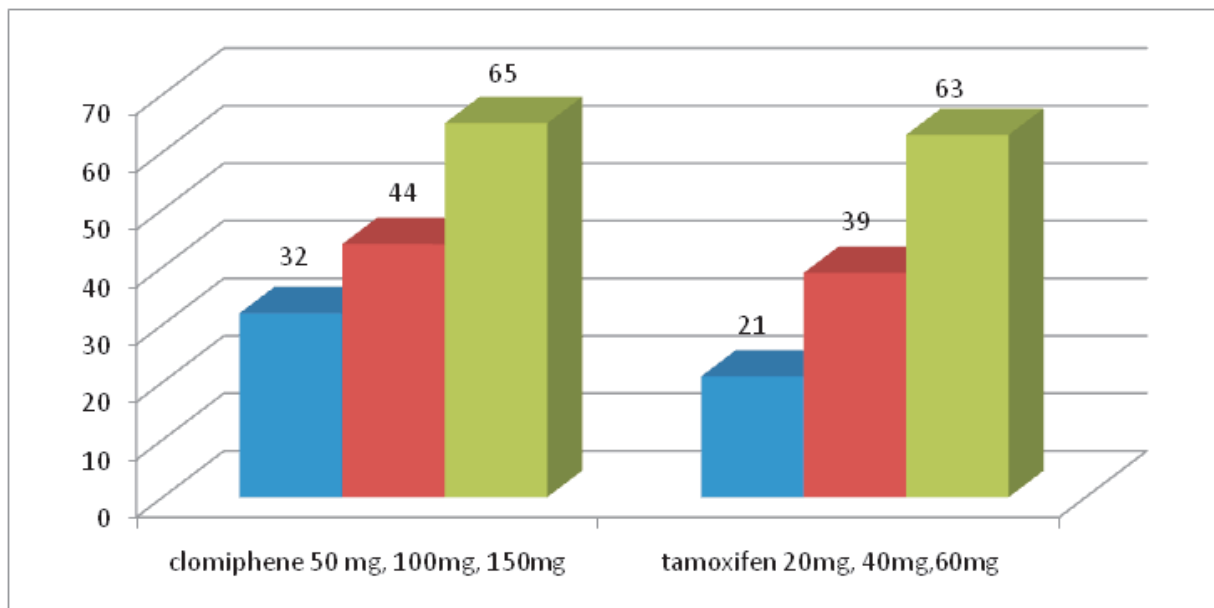


Figure 3. Drug doses and adequate follicle formation

Comparison of efficacy of two drugs in relation to the adequate size follicular development with different doses: (figure 2) While inducing ovulation with clomiphene citrate, 32 % of women had development of adequate size follicle after taking 50 mg of the drug in first time. Some of the women who had adequate size follicular development after taking 50 mg of clomiphene could not conceive. Some of them needed increased dose of the drug. From these failures and rest 68 percent who did not respond to 50 mg clomiphene, 44 % responded to 100 mg. Similarly, failures from these two groups, a total of 65% women

tamoxifen group, LH surge was positive in 62 % and 61 % cases respectively with p value of 0.76 (Figure 3).

Biochemical pregnancy when compared between CC 50 mg and TMX 20 mg, p value is 0.42; 100mg CC and 40 mg TMX, p value is 0.07; 150mg CC and 60 mg TMX, p value is 0.75 Clinical pregnancy, when compared between CC 50 mg and TMX 20 mg, p value is 0.12; 100mg CC and 40 mg TMX, p value is 0.05; 150mg CC and 60 mg TMX, p value is 0.47

Table1. Comparison of biochemical and clinical pregnancy rates.

	50mg CC	100mg CC	150mg CC	20mg TMX	40mgTMX	60mgTMX
	n=100	n=91	n=88	n=100	n=94	n=85
Biochemical pregnancy	9(9%)	3(3.3%)	5(5.7%)	6(6%)	9(9.6%)	6(7.1%)
Clinical pregnancy	8(8%)	2(2.2%)	3(3.4%)	3(3%)	8(8.5%)	5(5.9%)

had development of adequate size follicle after taking 150 mg of the drug. In the same way, in Tamoxifen group 29 % responded to 20 mg, 39 and 63 percent women responded to 40 mg and 60 mg respectively. Though there was adequate size follicle formation in 65 % cases of clomiphene and 63 % cases of

Discussion

Clomiphene citrate is the drug used first for ovulation induction in women with anovulatory infertility. Later on many other drugs like metformin, tamoxifen, bromocriptine, and gonadotropin are being used for this purpose.

Clomiphene and tamoxifen are of same group of drugs but tamoxifen has been used for ovulation induction only since last few years and there are not many studies for comparison of efficacy of these two drugs.

Though it is assumed that the women with regular menstrual cycles of 28-30 days are considered as ovulatory, but in this study, 28 percent of women with anovulation had regular menstrual cycle of 28-30 days. Women older than 35 years had less conception rate in both groups but the endometrial thickness was better in Tamoxifen group.

Robert Boostanfar, in a similar study [7], found 46% ovulation rates in Clomiphene group and 56.5 % in Tamoxifen group in comparison to 32 and 21 percent in this study. Cumulative pregnancy rate according to Boostanfar was 14.6 % and in this study it is 9 %.

According to another study done by Greenblat also the ovulation rates were quite higher than this study which was 80 and 40 % in Clomiphene and Tamoxifen group respectively [8]. According to a meta-analysis done by Anne Z Steiner and co-workers, Tamoxifen is equally effective as clomiphene for induction of ovulation [9]. But Ruiz-velasco V and co-worker found better ovulation rate in Tamoxifen group; 85.99% ovulation and 35.5 % pregnancy rate in clomiphene and 95% and 35.5% in tamoxifen group [10]. None of the studies had mentioned about the endometrial responses to these drugs. Hence, it can be concluded that tamoxifen is an equally effective alternative for induction of ovulation.

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