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A Comparative Study Between Clomiphene and Tamoxifen for Ovulation Induction

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Summary

A prospective study was conducted on 41 patients of anovulatory infertility attending the infertility unit of Queen Mary's Hospital, K. G. Medical College, Lucknow. Ovulation induction was done randomly by clomiphene (n=20) and tamoxifen (n=21). The effect of the two drugs were compared by six different parameters.

Significant difference between tamoxifen and clomiphene was observed in number of follicles attained (monofollicular 75%; 27.77% respectively), day of ovulation (15.64± 2.04; 12.66 ± 2.110); endometrial thickness (9.53±4.41 mm, 8.12 ± 3.70); periovulatory cervical mucus score (9.95±3.66, 5.82±5.86). Thus tamoxifen avoided, multi-follicular development, premature follicular rupture, had less antiestrogenic effect on the endometrium and cervical mucus. The crystallographic pattern of ferning of cervical mucus in tamoxifen treated cycle was atypical in structure inspite of being tertiary stage ferning. There was no significant difference between the maximum size of follicle attained and rate of ovulation. Thus tamoxifen is a better alternative antiestrogen as compared to clomiphene.

Introduction

Infertility due to ovulatory disorders is an easily treatable cause. Antiestrogens, like clomiphene and tamoxifen form an important medical mode of management of anovulatory infertility. These are competitive estrogen antagonists which displace estrogen from estrogen receptor binding protein in hypothalamic pituitary ovarian axis leading to decreased negative feedback of endogenous estrogen. It results in enhanced hypothalamic GnRH pulse generation activity augmenting follicular recruitment.

Clomiphene causes ovulation induction but its action, on endometrium and cervical mucus reduced the pregnancy rate inspite of a high ovulatory rate. Tamoxifen binds to estrogen receptor, but causes and imperfect confirmation change that results in an inability of the complex to initiate all the necessary estrogenic responses. Therefore, it acts as an antiestrogen but some estrogen regulated protein synthesis can be initiated, so it is called as partial estrogen agonist. Its use in ovulatory factor infertility therefore has certain advantages over clomiphene. It plays an important role in PCOS, and does not make cervical mucus unreceptive to sperm. It has no antiestrogenic action on the endometrium instead it acts as an estrogen agonist.

This study was therefore undertaken to compare the effects of clomiphene and tamoxifen for ovulation induction.

Material and Methods

Clomiphene was given in 50 mg dose from second day of periods for 5 days. If there was no response, the dose was increased to 100 mg in the next cycle and 150 mg in the subsequent cycle. Tamoxifen was given in dosage of 20 mg in same manner as clomiphene which was increased to 40 mg in absence of response. The

results were therefore compared in 58 clomiphene and 43 tamoxifen cycles.

TV sonography was used for follicular monitoring to determining the :

- Number of follicles recruited in an ovulatory cycle
- Maximum size of follicles attained which is the mean diameter of follicle in two dimensions
- Occurrence of ovulation
- Day of ovulation
- Endometrial thickness and pattern

Periovulatory cervical mucus scoring was done to see the condition of cervical mucus. Cervial mucus was collected from the endocervix by means of disposable 1 ml tuberculin syringe. Score was calculated by means of table 1

Ferning of cervical mucus which is an indicator of the level of estrogenic activity at level of cervix was observed under microscope and its crystallographic structure observed.

The results were then compared and statistical significance calculated by "Chi square test" and "Student's test".

Results

The maximum size of the follicle attained in clomiphene treated cycle was 18.17±5.76 mm which was not significantly different from tamoxifen treated cycles i.e. 18.11±6.32 mm (t=0.048; p>0.05).

The number of follicles recruited in clomiphene treated cycle was more than on in 72.22% of cases which was significantly different from that in tamoxifen treated cycle i.e. 25% (X^2 = 20.54; p<0.005).

Rate of ovulation in tamoxifen treated cycle (72.09%) was significantly different than in clomiphene treated cycle (58.6%) (X^2= 1,941; p>0.05).

Average days of ovulation in patients treated with clomiphene was about 12.66± 2.10 days and proves that clomiphene causes premature follicular rupture. Tamoxifen causes rupture on 15.64 ± 2.04 days and the difference between the two was highly significant (t=6.47; p<0.005).

Endometrial thickness decreased under the effect of clomiphene citrate (8.12 ± 3.70) while that under tamoxifen treatment was significantly better (9.53 ± 4.41) (t=1.71; p<0.04)

Only 1 conception occurred in 58 clomiphene cycles while there were 2 conceptions in 43 tamoxifen stimulated cycles.

Periovulatory cervical mucus score was higher

Table I : Cervical Mucus Scoring

	0	1	2	3
Amount	None	Scant	Dribble	Cascade
Spinbarkeit	0-2	3-6	7-10	7 - 10
Ferning	None	Linear	Partially branched	Completely Branched
Viscosity	Thick	Medium	Medium thin	Very thin
Condition of cervix	Closed		Open	Gaping

Table II : Comparison between clomiphene and tamoxifen

	Clomiphene	Tamoxifen	p value
Maximum size of follicles attained follicles attained	18.17 ± 5.96	18.11± 6.32	t=0.048; p>0.0
Rate of follicular rupture	58.6%	72.09	X^2 = 1.941; p>0.05
Number of follicles recruited	Monofollicular 27.77%	Monofollicular 75%	X^2 =20.54; p<0.005
Days of follicular rupture	12.66± 2.10	15.64 ± 2.04	t=6.47; p<0.005
Endometrial thickness	8.12 ± 3.70	9.53 ± 4.41	t =1.71; p<0.05
Periovulatory cervical mucus score	5.82± 5.86	9.95 ± 3.66	t = 4.44; p<0.005

in tamoxifen treated cases (9.95±3.66) as compared to clomiphene treated cases (5.82±5.86) (t=4.44; p<0.05).

The crystallographic pattern of ferning observed in tamoxifen treated cycles was atypical in structure inspite of the marked estrogenic activity evident by tertiary stage ferning in most of the tamoxifen treated cycles.

No evidence of ovarian hyperstimulation or any other side effect was noticed in either of the treatment cycles. He results have been compared in Table II.

At the end, it is concluded that tamoxifen is a better alternative antiestrogen as compared to clomiphene as ovulation inducing agents for use in anovulatory infertility.

Discussion

Till date, no study has compared the maximum size of follicle attained and the number of follicles recruited in the two cycles. This study was therefore an effort to bring this difference into light. Clomiphene has for a long time been held responsible for multiple pregnancies. Tamoxifen avoids this by causing monofollicular development.

Two studies have compared the rate of ovulation in the two treatment groups, clomiphene and tamoxifen. Ioannis and Seven (1982) also found no significant difference in the ovulation rate between the two groups as in our study. However, R. Borenstein. Z. Shoham & M. Yemini (1989) found the ovulation rate significantly increased as compared to clomiphene.

Clomiphene is known to cause premature follicular rupture for a long time and this has been proved by our study. Tamoxifen avoids it as shown in this study.

Several studies show the effect of clomiphene on endometrial thickness. Fleischer et al. in 1984, Eden and Jones in 1989 and Randal & Templeton in 1991 all show the antiestrogenic activity of clomiphene on endometrium. Our study found a reduction in endometrial thickness by clomiphene which can be avoided if tamoxifen is used. The difference was found to be significant.

Antiestrogenic effect of clomiphene on cervical mucus caused hostile cervical mucus. This study used mucus only at the point of maximal receptivity i.e. periovolutory cervical mucus confirmed by transvaginal sonography. Previous studies that have demonstrated adverse effects of clomiphene have drawbacks including use of anovulatory control cycles and grouping of data from different cycle days; possible residual effects of antiestrogens in placebo cycles. Tepper et al. (1988); Acharya and Hamilton (1993) and Annapurna (et al, 1997) all found a similar results as in our study.

Ferning of cervical mucus is an indicator of estrogen activity at the level of cervix. It is due to presence of sodium chloride in the mucus secreted under estrogenic activity. Polarising microscopy and conventional X-ray devices show these fern like microstructures to be very complex. The core of the dendrites appear to be composed of NaCI and also KCl and appear under polarising microscope as isotopic crystals. Anisotropic structures can be observed at the periphery of the dendrites or isolated as small spheroliths. They are composed of double salts of potassium and sodium. The K/Na cation ratio equal to 3/1 remains constant in the best specimen.

In our study, ferning observed was upto tertiary stage in most of tamoxifen treated cycle but it was atypical in structure. Further, crystallographic studies are needed to detect the cause of this structural change seen with tamoxifen. Till date no study has brought this difference due to clomiphene and tamoxifen into light.

This study was thus an effort to compare the effect of clomiphene and tamoxifen over different parameters required for a fruitful result of ovulation induction i.e. conception and proves that tamoxifen is better alternative antiestrogen as compared to clomiphene.

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