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RESEARCH PAPER

Ovulation Induction: A Comparison between Clomiphene and Tamoxifen

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ABSTRACT

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

There was a significant difference between tamoxifen and clomiphene in number of follicles attained (monofollicular 75%, 27.77% respectively), mean day of ovulation (15.64±2.04; 12.66±2.110); endometrial thickness (9.53±4.41 mm, 8.12±3.70) and periovulatory cervical mucus. The crystallographic pattern of ferning of cervical mucus in tamoxifen treated cycle was atypical in structure inspite of being tertiary stage ferning. When the maximum size of follicle attained and rate of ovulation were compared, there was no significant difference. Thus tamoxifen is a better alternative antiestrogen as compared to clomiphene.

Keywords: Clomiphene, Tamoxifen, Estrogren, Ovulation and Endometrium.

INTRODUCTION

Anovulatory infertility is an easily treatable cause of infertility. It can be medically treated by group of compounds known as anti estrogens. Anti estrogens like clomiphene and tamoxifen are competitive estrogen antagonists who displace estrogen from estrogen receptor binding proteins in hypothalamic pituitary ovarian axis leading to decreased negative feedback of endogenous estrogen. This leads to enhanced hypothalamic GnRH pulse generation activity augmenting follicular recruitment.

Clomiphene causes ovulation induction but its action, on endometrium and cervical mucus reduces the pregnancy rate in spite of a high ovulatory rate. Tamoxifen binds to estrogen receptor, but causes an imperfect conformational change that result in an inability of the complex to initiate all the necessary estrogenic responses. Therefore, it acts as an anti estrogen 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 anti estrogenic 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. Cervical mucus was collected from the endocervix by means of disposable 1 ml tuberculin syringe. Score was calculated as in 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 was noticed.
The results were then compared and statistical significance calculated by "Chi square test" and "Student't- 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 ($t=0.048$; $p>0.05$).
Out of 50 cases in study group, 8 were in follicular phase. So serum progesterone was measured in only 42 cases. It can be seen that out of total 42 cases, 6 had luteal phase defect which was 14.28% whereas in control group only 3 cases 10% had luteal phase defect. This difference is insignificant. Thyroid abnormality was seen in 1 out of 50 patients in study group i.e. 2% while in control none had thyroid dysfunction. This is also insignificant. Blood sugar derangement was seen in 1 out of 50 patients in study group i.e. 2% while in control group none had blood sugar abnormality. This is an insignificant difference (Table 1, 2 and 3).
By this table it is clear that incidence of LPD, thyroid abnormality and blood sugar abnormality is similar in both control and study group but incidence of hyperprolactinemia is more in study group as compared to control group (Table 4).

DISCUSSION

Risk of spontaneous abortion for a woman with no history of reproductive wastage is about 15%. After first spontaneous abortion, the chance for a repeat abortion is 19% and with 2 spontaneous abortions the risk increase to 35%. With 3 previous spontaneous abortions, the risk of repeated abortions is 47%.

The main aim of our study was to establish "the role of hyperprolactenimia as one of the causes of spontaneous abortions". It was seen that hyperprolactinemia is found in 17 % of the cases in study group which is higher than that in contril group (6.6%). Similar study was done by Hirahara and Anodh, 1998. They evaluated the role of hyperprolactinemia in the pathogenesis of recurrent spontaneous abortions and measured the rate of successful pregnancies after restorations of prolactin level with bromocriptine. It was seen that the percentage of successful pregnancies was higher in bromocriptine treated group than in the group that was not treated with bromocriptine (85.7% versus 52.4%, $p<0.05$). Serum prolactin levels during early pregnancy (5-10 weeks of gestation) were significantly higher in patients who miscarried (31.8-55.3 μg/ml) then in patients whose pregnancies were successful (4.6-15 ng/ml, $p<0.01$ or $p<0.05$).

Chung Hua et al., 1993, in their study indicated that prolactin might be associated with luteal function during early pregnancy. Baituraeva and Zheinkulova, 1984, in their study showed that in hyperprolactinemia the level of LH secretion was high the level of LH was moderately increased during all phases of menstrual cycle. Secretion of FSH similar in both groups, Rossi et al. 1995, evaluated the outcome of pregnancies in women with treated or untreated hyperprolactinemia. They found that obstetrical complications like miscarriages and tubal pregnancies are more in women with untreated hyperprolactinemia. Thus, all these studies indicate that prolactin has a role in recurrent spontaneous abortion indirectly by causing luteal insufficiency or by LH dysfunction.

Day et al. studied progesterone profile in LPD cycles in patients with recurrent spontaneous abortions. The incidence of luteal phase defect was 40% in women with recurrent abortions in their study and 81% of pregnancies were successful with treatment. In our study the difference between the two groups was insignificant.

Measurement of TSH and free thyroxine are almost routine in patients with a history of repeated pregnancy losses. However, it is rate that a deficiency or an excess of thyroid hormone is the etiology of early pregnancy loss. Patients with thyroid dysfunction are affected instead by preterm labor usually occurring after 24 weeks.

No statistically significant difference was seen serum T3, T4 and TSH values in study and control groups (p=0.3156) in our study.

Controversy surrounds the questions of whether the women with insulin dependent diabetes have a higher than normal risk of spontaneous abortion. Studies by Crane and Wahe, 1981, have shown that diabetes is not a cause of early pregnancy loss. However, a large multicentre controlled study by Mills et al, 1988, found the diabetes with both an elevated blood glucose and hemoglobin in the first trimester have a significantly increased risk of abortion, whereas those with good metabolic control had a risk similar to that of control subjects.

Our study showed no significant difference between the blood sugar values of the study and control subjects (p=0.4656).

Table 1

Reference group	Median (ng/ml)	Central 95% range
Non-pregnant	6.2	ND - 20
1st trimester	17	7-31
2nd trimester	118	31-182
3rd trimester	120	84-232
1 day postpartum	157	20-319

Table 2

	Study Group (A)		**Control Group (B)**	
	Number of hyper Prolactinemic cases	**%**	**Number of hyper Prolactinemic cases**	**%**
Pregnant cases	14	28	2	6.6
Non-pregnant cases	3	6	0	0
Total	**17**	**34**	**2**	**6.6**

X^2= 7.7354; p=<0.001

Table 3

Pregnancy losses	Total number cases in Group A	Total number of cases with hyperprolactinemia	%
PO+1	3	0	0.00
PO+2	26	11	42.30
PO+3	13	4	30.76
PO+4	5	0	0.00
PO+5	1	1	100.00
PO+6	2	1	50.00

***X^2 =0.7923;* p=>0.05 (NS)**

Table 4

Endocrinal markers	Study Group		Control Group		Significance
LPD	6 (n=42)	14.28%	3 (n=30)	10%	X^2=0.2938,
					p≥0.05 (NS)
T3, T4,	1 (n=50)	2%	0	0	X^2=0.61,
TSH					p=0.3156
abnormality					(NS)
Blood	1 (n=50)	2%	0	0	X^2=0.061,
sugar					p=0.4656
abnormality					(NS)
hyperpro-lactimenia	17 (n=50)	34%	2 (n=30%)	6.6%	X^2=7.7354, p<0.001 (significant)

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