ORIGINAL STUDY

Beneficial Effects of Addition of Glucocorticoid during Induction of Ovulation by Letrozole in Polycystic Ovarian Syndrome

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ABSTRACT

Objective: The aim of the study was to explore the efficacy of glucocorticoid in folliculogenesis and ovulation during induction of ovulation by letrozole in polycystic ovarian syndrome (PCOS).

Materials and methods: This experimental study was conducted in Dhaka Medical College and Hospital and Infertility Care and Research Centre (ICRC) Dhaka, Bangladesh. Two hundred and eighty infertile patients with PCOS, who failed to ovulate by letrozole 10 mg/day for 5 days were the target population of this study. The patients received glucocorticoid (Dexamethasone) 0.5 mg every alternate day from D2 of the cycle till D10 along with same dose of letrozole in subsequent cycles. Only letrozole-treated cycles were taken as control and letrozole plus glucocorticoid-treated cycles were taken as experimental. Monitoring was done by transvaginal ultrasonography. Six ovulatory cycles were observed for pregnancy. Main outcome measures were ovulation and pregnancy.

Results: Baseline characteristics were similar as same patients were taken as control and experimental. One hundred and eighty-two (65%) patients were ovulated and 93 (33.21%) patients got pregnant after addition of glucocorticoid.

Conclusion: In PCOS addition of glucocorticoid during induction of ovulation appears to cause significant improvement in folliculogenesis, ovulation and pregnancy.

Keywords: Polycystic ovarian syndrome, Induction, Glucocorticoids, Ovulation, Pregnancy.

INTRODUCTION

Anovulation is the main cause of infertility in polycystic ovarian syndrome (PCOS) and different biochemical factors are associated with this abnormal function. Chronic hyperandrogenism is the principal biochemical abnormality in women affected by PCOS and is often attributed to enhanced biglandular androgen production by both the ovaries and the adrenals.[1] Even in insulin resistance women, ovaries and adrenal cortex may remain insulin sensitive and may produce excess androgen in response to excess circulating insulin. In women with PCOS ovarian androgen synthesis is increased and in 50 to 70% cases there is a concomitant increase in adrenal synthesis. Most potent androgen is testosterone and slight increment of free testosterone causes significant hyperandrogenism. Fifty percent testosterone comes from peripheral conversion of androstenedion and 50% androstenedion comes from adrenal gland.

Hyperandrogenism is associated with varying degrees of ovulatory dysfunction and infertility. As plasma androgen levels increase, the length of the follicular phase of menstrual cycle increases and length of the luteal phase decreases. It causes follicular atresia and formation of ovarian cysts of varying sizes. The cysts represent the end results of disturbed follicular development and rupture. This ovulatory dysfunction due to hyperandrogenemia has been experimentally demonstrated to occur after administration of progressively increasing doses of testosterone to normally ovulating females.[2] Hyperandrogensim also has been associated with a decreased progesterone production by corpus luteum causing luteal phase deficiency leading to implantation failure and increased incidence of abortion.[3,4]

Glucocorticoids reduce adrenal androgen production by negative feedback inhibition of adrenocorticotrophic hormone production. So the administration of low doses of glucocorticoids may be of benefit to women with hyperandrogenic anovulation. The mechanism of action presumably involves a reduction in adrenal androgen secretion which may reduce total circulating androgen levels by as much as 40%.[5-7] As a result of reduction of androgen to some extent folliculogenesis might be improved. So aim of this study was to explore the efficacy of glucocorticoids in folliculogenesis by reducing androgen to some extent in PCOS.

MATERIALS AND METHODS

This experimental study was conducted in outpatient Department of Dhaka Medical College and Hospital and Infertility Care and Research Centre, Dhaka from January 2009 to June 2011. PCOS patients were treated by letrozole with gradual increment of doses starting from 5 mg/day for 5 days. PCOS were diagnosed by Rotterdam criteria. Four hundred and seventy patients were treated by aromatase inhibitor (letrozole) upto 10 mg/day for 5 days starting from D3 of the natural or progesterone withdrawal cycle. Those patients who did not respond to this high dose of letrozole were recruited for addition of glucocorticoid in subsequent cycles. One hundred and ninety of them ovulated with letrozole 10 mg/day but rest 280 did not develop mature follicle till day 16 of the cycle. In next cycle dexamethasone 0.5 mg every alternate day from D2 of the cycle till D10 was added along with letrozole. Monitoring was done by (i) transvaginal sonogram (TVS) from

D12 to D16 of the cycle, (ii) S E2 level on last day of monitoring and (iii) S P4 level on D21. All patients' basal hormone was measured on D3 of the cycle. Serum testosterone was measured again on D8 and D12 of both letrozole-treated and letrozole plus dexamethasone-treated cycles. Same patients' letrozole-treated cycle was taken as control and letrozole plus dexamethasone-treated cycle was as experimental. Once patient's ovulation was confirmed by observing rupture or collapse of the mature follicle she received same regimen for next five cycles to complete six ovulatory cycles. Main outcome measures were ovulation and pregnancy. Abnormal semen parameters, known or suspected tubal factor abnormality (PID with chronic pelvic pain), were excluded. Mean ± SD and Student's t-test was done for test of significance. A p-value <0.05 was considered as significant. The study was approved by the institutional review board of Dhaka Medical College.

RESULTS

As same patients were taken as control and experimental the baseline parameters like age, BMI, FSH, LH, E2, TSH, prolactin, DHEAS, 17aHOP, total and free testosterone were same in both control and experimental cases (Table 1).

Table 2 shows the changes of free testosterone after administration of glucocorticoid. In experimental group there

Table 1: Patients' characteristics

Characteristics	Mean ± SD
Age (yrs)	25.47 ± 3.98
BMI (kg/m^2)	23.63 ± 3.23
FSH (mIU/ml)	5.79 ± 1.60
LH (mIU/ml)	8.73 ± 2.15
E2 (pg/ml)	
TSH (mIU/ml)	4.63 ± 0.32
Prolactin (ng/ml)	23.40 ± 4.9
DHEAS (ng/ml)	1971 ± 1086
17aHOP (ng/ml)	2.3 ± 1.25
Total testosterone (ng/dl)	83.9 ± 45.4
Free testosterone (ng/dl)	0.53 ± 0.43

was slight reduction of free testosterone level which is not statistically significant. In spite of nonsignificant reduction of testosterone ovulatory result was satisfactory in experimental group. One hundred and eighty-two (65%) patients, who previously did not ovulate by only letrozole ovulated after addition of glucocorticoid (Table 3). Ninety-three (33.21%) patients got pregnant after establishing ovulation.

DISCUSSION

Adrenal androgen excess in the form DHEAS affects approximately 50 to 70% of women with PCOS.[8-10] The role of adrenal hyperandrogenism in producing the PCOS associated oligo-ovulation is not clear, as both dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are relatively weak androgen in comparison to testosterone (T).[11] However, circulating DHEAS has been found to be the precursor for almost 50% of the follicular fluid T in women treated with menotropin.[12] Fifty percent androsterone comes from adrenal gland. So 50% intrafollicular T come from adrenal gland. This elevated intrafollicular androgens have been associated with an increased incidence of follicular atresia, polycystic like ovaries and ovulatory dysfunction.[13,14] With this presumption that adrenal androgen excess play a role in the ovulatory dysfunction of women with PCOS a number of investigators have noted a beneficial effect of glucocorticoid administration on ovulation. The first case in which a glucocorticoid was used for hyperandrogenism was reported in 1950 by Wilkins et al,[15] Bartter et al (1951)[16] showed that cortisone can reduce excess androgen production by adrenal gland. These fundamental studies laid the ground work for all subsequent investigatons of pathophysiology and glucocorticoid therapy in hyperandrogensim. The beneficial effect of cortisole treatment in patients with ovulatory dysfunction was reported by Jones et al in 1953[17] and a 30% incidence of pregnancy was observed by Greenblat et al in 1956.[18] Perloff et al and Smith et al in 1965 demonstrated the effectiveness of cortisone in a large group of patients with infertility and PCOS.[19,20] In

Table 2: Free testosterone changes after dexamethasone use

Free testosterone	Control (280) Mean ± SD	Study (280) Mean ± SD	Reduction (%)	p-value
On D3 (ng/dl)	0.53 ± 0.43	0.53 ± 0.43	Same	
On D8 (ng/dl)	0.69 ± 0.65	0.54 ± 0.51	21.73	0.525
On D12 (ng/dl)	1.24 ± 1.49	0.81 ± 0.72	34.67	0.225

Table 3: Response to treatment

Parameters	Control (280) Mean ± SD		Study (280) Mean ± SD		p-value
Follicular development (mm) by D16	14.4 ± 2.89		20.12 ± 3.47		<0.001*
S E2 (pg/ml) by D16	110 ± 98.75		520.75 ± 256.70		<0.001*
End (mm) by D16	6.5 ± 0.89		11.21 ± 1.5		<0.001*
SP4 (ng/ml) D21	3.12 ± 0.97		21.98 ± 12.11		<0.001*
	N	%	N	%	
Ovulation	00	00	182	65.00	000**
Pregnancy	00	00	93	33.21	000**

*Significant; **Highly significant

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hyperandrogenic patients with ovarian dysfunction, reduction of circulating androgen levels is associated with progressive improvement in ovulatory activity.[21] The improvement is slow process and eventually normal ovulatory cycles may be established. The extent of improvement of the ovulatory function has been shown to be directly correlated to the degree of suppression of circulating testosterone levels.[21] Steinberger et al has shown progressive improvement in ovulatory activity with glucocorticoid treatment.[22] In a majority of hyperandrogenic women androgen levels can be suppressed with low dose glucocorticoid treatment.[21,23] How does glucocorticoid improve ovulatory dysfunction? Glucocorticoids reduce total circulating androgen levels as much as 40%[5-7] as well as low-dose glucrticoid treatment may enhance FSH synthesis and secretion.[24,25] The combination of reduced androgen concentrations and augmented FSH secretion may induce responsiveness of drugs in a previous nonresponder. It is not only effective in hyperandrogenic women[6,7,24,26] but also has been shown to be effective in CC resistant women with normal levels of DHEAS.[6,25]

In our series we also found effective result by using low-dose glucocorticoid therapy even with normal androgen levels. Eighty percent patients ovulated after administration of low-dose glucocorticoid along with letrozole therapy. A number of authors shown that effectiveness of clomiphene citrate were improved when the circulating androgen levels were suppressed with glucocorticoids.[6,7,24-27] Even in hyperandrogenic women unresponsive to clomiphene citrate, pretreatment with glucocorticoids to suppress androgen levels results in establishment of an ovulatory response to clomiphene citrate.[26] Same happened in our study though initial ovulation inducing agent was letrozole instead of clomiphene citrate. In our previous study we found better ovulatory response by letrozole than clomiphene citrate.[28] So we used letrozole as first-line treatment in these cases. Azziz R showed that only 12% cycles were ovulatory with glucocorticoid therapy,[29] others did not ovulate. It was the result of only glucocorticoids. That is why he concluded that corticoid suppression may enhance the ovulatory response to clomiphene citrate. Although ovulation and conception may occur with single-agent low-dose glucocorticoid therapy, most patients will also require the addition of ovulation inducing agents. A number of authors declared that glucocorticoid resulted in significant suppression of all androgens in PCOS patients.[30-36] Although elevated intrafollicular levels of T appear to be associated with PCOS,[37,38] Azziz's data suggest that solely reducing circulating T levels is insufficient to normalize ovulatory function. So it will be very effective when it is used along with CC or other ovulation inducing agent. We used corticosteroid in very low dose for a short period of time to reduce androgen during folliculogenesis, so that negative effect of androgen in follicular development is withdrawn. The adverse effect of prolonged use of supraphysiolosical doses of glucocorticoids are numerous[39-41] like effect on eyes, bones, immune system or on protein, carbohydrate and lipid metabolism. But the side effects, if any of physiological replacement doses of glucocorticoids

used for treatment of hyperandrogenism are less well defined. We did not found any side effect in our series by administration of glucocorticoids. We used dexamethasone 0.5 mg till D10 and measured free testosterone on D3 before starting the drug and on D8 and D12. The free testosterone was reduced by 21 and 34% on D8 and D10 respectively. Though the reduction was not statistically significant the ovulatory response was satisfactory. So it indicates that a slight reduction of androgen is helpful for optimum folliculogenesis. In letrozole-treated cycles there may be slight accumulation of androgens as letrozole inhibits aromatization of androgens. But recent data support a stimulatory role for androgens in early follicular growth in primates.[42] In addition, androgen accumulation in the follicle may stimulate insulin-like growth factor 1, and other endocrine and paracrine factors, which may synergize with FSH to promote folliculogenesis.[43-45] So it has dual role in different concentration. Therefore, optimum concentration is necessary for optimum and effective follicular growth. Keeping this in mind we used glucocorticoids in very low doses so that androgen reduces slightly. Moreover, to avoid side effects of glucocorticoids we used only cyclically during follicular development. Trott et al reported success with follicular phase dexamehasone (D3-D12) in CC resistant women with normal DHEAS levels.[25]

We kept same patients as control and experimental to avoid the effect of confounding variables like age, BMI, etc. One hundred and eighty-two (65%) patients produced mature follicle by D16 when we added glucocorticoids in next cycle. Patient received same regimens for next five cycles to complete six ovulatory cycles. Ninety-three (33.21%) got pregnant within observation period.

Ovulation induction is necessary for most of the PCOS patients. Twenty-five percent patients are usually very resistant to ovulation inducing agents. They need higher dose of ovulation inducing agent even higher dose of gonadotropins. Usually they do not produce eggs with ordinary drugs, on the other hand they produce multiple eggs with gonadotropins. So it is an art to induce PCOS patient to produce optimum number of eggs. If we are able to use endogenous gonadotropins for stimulating the ovaries and minimize the endogenous adverse factors optimum number of follicular development with full maturity is possible. Our trial proved that we can avoid using exogenous gonadotropins for most of PCOS, which can reduce the cost and risk of stimulation. For some cases, if gonadotropins added with this regimen requirement of gonadotropins also reduced. Most people like to do laparoscopic ovarian drilling (LOD) or use gonadoropin when ovulation does not take place by maximum dose of clomiphene citrate and letrozole. LOD is an invasive procedure and has cost involvement. Gonadotropin is also expensive and risky as well. So, if we could avoid these two things the treatment of PCOS will be cheaper, safer and easier. Because drugs are cheaper, safer and it does not need extensive monitoring during induction.

Use of glucocorticoids as adjuvant of ovulation inducing agent is safe, economic and effective for PCOS patients. It can

eliminate the use of invasive LOD and risky gonadotropins in most of the PCOS cases. Therefore, by using an individualized treatment protocol PCOS women can achieve a satisfactory ovulatory response, which is safe, economical and time honored.

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