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Gonadotrophin treatment in patients with Polycystic Ovary Syndrome

Dr. Majida Hameed Rasheed
University of Diyala, College of Medicine

Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder. It is characterized by hyperandrogenism, chronic anovulation, and is related to infertility, hirsutism, increased risk of insulin resistance, type 2 diabetes, cardiovascular disease and endometrial cancer. Pathophysiology of the syndrome appears to be multifactorial and polygenic.
Objective: To see the effect of gonadotrophin treatment in clomiphen citrate resistant polycystic ovary syndrome patients.
Materials and methods: 100 patients for one year from July 2007- July 2008 with polycystic ovary syndrome subjected to the following investigations, -serum LH, serum FSH, serum prolactin, serum progesterone, serum estradiol, ultrasound, serum testosterone. The work up implicate a simple clinical history, physical examination, laboratory investigation and ultrasound to see the effect of gnadotrophin treatment in ovulation induction.
Results: results obtained from this study pointed out the beneficial role of gonadotrophin treatment in clomiphene citrate resistant polycystic ovary syndrome patients.
Conclusions: It can be concluded that gonadotrophin treatment can be used reliably for ovulation induction in clomiphene citrate resistant polycystic ovary syndrome patients.

Keywords: polycystic ovary, gonadotrophin.

I. Introduction

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder. It is characterized by hyperandrogenism, chronic anovulation, and is related to infertility, hirsutism, increased risk of insulin resistance, type 2 diabetes, cardiovascular disease and endometrial cancer. Pathophysiology of the syndrome appears to be multifactorial and polygenic. Patients with PCOS display heterogencity with respect to clinical presentation, biochemical features and metabolic abnormalities [1].If there is a follicle > 10 mm in diameter, the scan should be repeated at a time of ovarian quiescence in order to calculate volume and area. The distribution of follicles and a description of the stroma are not required in the diagnosis. Since the main reason for infertility is anovulation in patients with PCOS, restoration of ovulation is undertaken when fertility is desired. The aim of ovulation induction in women with PCOS is the formation and ovulation of a single dominant follicle [2].

The following end-points should be considered when evaluation the safety and efficacy of ovulation induction in patients with PCOS,[3] single follicle development rate, multiple follicle development rate, multiple pregnancy rate, ovarian hyperstiulation syndrome (OHSS) rate, ovulation rate per cycle, pregnancy rate per cycle, miscarriage rate, singleton live birth rate per cycle and cumulative singleton live birth rate singleton live birth rate per cycle and

cumulative singleton live birth rate should be considered as the 'golden' outcome parameters for induction of ovulation[4].

Protocols for gonadotrophin treatment, It is essential for the infertility practitioner to recognize the importance of the FSH threshold concept for monofollicular development.

Conventional protocol, chronic low dose protocols, which include: Low dose step –up protocol, Low dose step –down protocol [5].

II. Materials and Methods

Atotal of 100 women who were recruited form the department of obstetrics and gynaecology in cooperation with department of laboratory in Basrah Maternity and child hospital during the period from June 2007 to June 2008.

The hospital chads of clients who presented at the infertility clinic were checked for the frequency number and type of gonadotrophins injection used, as well as the questionnaire form was used for the details regarding past obstetric and gynecological history, and for the past medical and surgical history.

Relevant data included the demographic data, women`s age, weight, height, BMI, type of infertility (primary or secondary), clinical signs of PCOs such as obesity, acne, hirsutism.

Biochemical tests of PCOs which include FSH, LH, prolactine and testosterone level, serum estradiol, serum progestron.Ultrasound signs of PCOS.

Venous blood sample withdrawn in early follicular phase of the menstrual cycle in eumenorrhoeic or oligomenorrhoeic women, for FSH, LH and sent to the lab. Another sample was taken on day 11 or day 12 of the cycle for estimation of serum estradiol. Another sample of blood was taken on day 21 of the cycle for estimation of serum progesteron also samples for serum prolactine and serum testosteron. All biochemical tests were done twice one as baseline before treatment, and another samples done after receiving gonadotophin lnjections.

III. Results

Descriptive Statistics (base line), before treatment is shown in table 1.

Table 1. Descriptive Statistics (base line)

	N	Mean	Std. Deviation
FSH	100	6.8091	6.91539
LH	100	7.4005	5.50335
PROLACTI	100	16.8422	12.63305
PROGESTERON	100	4.9948	6.50776
OESTRADIOL	100	91.2872	40.40019
TESTOSTERON	100	.2628	.34715
AGE	100	28.6000	5.13849
ULTRASOUND	0		
PRIMARY	0		
SCONDARY	0		
INFERTILITY	100	4.1400	2.92851
BODY MASS INDEX	100	23.3160	4.11260
Valid N (listwise)	0		

Descriptive Statistics (after treatment) is shown in table 2. The clinical and endochine features of PCOs patients (ongoing study) as in Table 3. Values are means ± SD. Range given in parenthesis.

The total number of patients are 100 and the number of cycles are 220. Duration of infertility in years are 4.14 ± 2.9 (1-16).

Table 2. Descriptive Statistic (After treatment)

	N	Mean	Std. Deviation
FSH	100	6.4899	5.30969
LH	100	6.2125	3.93023
PROLACTI	100	14.5882	14.47523
PROGE	100	13.3358	11.68305
OESTRADI	100	153.5200	74.36903
TEST	100	.2628	.34715
AGE	100	28.6000	5.13849
MASS	100	23.3160	4.11260
Valid N (listwise)			

Table 3. Clinical and endocrine features of PCOS patients (ongoing study). Values are means ± SD. Range given in parentheses.

No. of patients	100
No. of cycles	220
Duration of infertility (years)	4.14 ± 2.9 (1-16)
Mean female age (years)	28.6 ± 5.1 (1843)
Body – mass index (kg/^{m2})	23.3 ± 4.1
LH (IU/1)	7.4 ± 5.5 (0.1-29.3)
Testosterone (ng/dl)	0.26 ± 0.3 (0.1- 3.4)
Anovulatory with Clomiphene citrate (%)	49

The mean female are in years are 28.6 ± 5.1 (18 -43).

Body mase index (kg/m^2) are 23.3 ± 4.1.

LH (IU/L) 7.4 ± 5.5 (0.1-29.3)

Mean testosterone (ng/dl) level is 0.26 ± 0.3 (0.1-3.4).

FSH (IU/L) 6.8 ± 6.9 (0.6-47.30)

Table 4. The results of experience on low dose step-up protocols using recombinant FSH in 100 patients in (220 cycles), as below

Table 4. Results of low dose step up protocol (ongoing study). Values are means ± SD. Range given in parentheses unless otherwise stated.

-	Cycle cancellation (%)	20
-	Hyper – response (%)	4
-	No response (%)	10
-	Threshold FSH (dose) (IU/day)	112.8±45.04 (38-300)
-	Duration of stimulation	14 days
-	Estradiol on day of hCG (pg/ml)	153.5±74.3 (506-587.5)
-	No. of ovulatory cycles	(47) %
-	No. of pregnancy	(29)%
-	No. of multiple pregnancies	8

No. of cycle cancellation 20 %, Hyper – response 4 %, No response 10%,

Threshold FSH (dose) (IU/day) 112.8 ±45.4 (38-300),

Estradiol on day of hCG (pg/ml) 153.5 ± 74.3 (506-587.5)

No. of ovulatory cycles 47 %, No. of pregnancy 29%,

No. of multiple pregnancies 8.

IV. Discussion

Since the main reason for infertility is anovulation in patients with PCOS, restoration of ovulation is undertaken when fertility is desired. The aim of induction of ovulation in women with PCOS is the formation and ovulation of a single dominant follicle [6].

The following end points should be considered when evaluating the safety and efficacy of ovulation induction in patient with PCOS: single follicular development rate, multiple follicle development rate, multiple pregnancy rate, ovarian hyperstimulation syndrome (OHSS) rate, ovulation rate per cycle, miscarriage rate, singleton live birth rate per cycle and cumulative singleton live birth rate should be considered as the 'golden' outcome parameters for induction of ovulation [7].

While several approaches for ovulation induction with gonadotrophins have been described, the two most commonly used in the clinical practice are the low-dose step-up and the low-dose step-down protocols. These chronic low-dose protocols should be applied for gonadotrophins to minimize the risk of multiple follicular development. The two risks associated with multiple follicular development are multiple pregnancy and OHSS.

The conventional protocol, which is associated with unacceptable high multiple follicle development, multiple pregnancy and significant incidence of OHSS,[8] should not be employed to induce ovulation in patients with PCOS.

In order to minimize the rate of multifollicular development, chronic low dose protocol should be employed [9]. The chronic low dose protocols include, low dose step-up protocol, low dose step-down, sequential protocol.

Low dose step-up protocol is most commonly employed chronic low dose regiment, & the one which employed in this study. This protocol is employed as follow after spontaneous or progesterone induced withdrawal bleeding,75 IU of daily FSH treatment is commenced The initial dose of FSH of 75IU/day is maintained for up to 14 days unless follicular maturity is reached so that human chorionic gonadotrophins (HCG) could be administered[10][11][12][13]. The multiple pregnancy rate may be minimized by strict adherence to the criteria for administrating HCG. In spite of the strict criteria in administering HCG our result of multiple pregnancy rate was higher than that reported[14]. He reported 4% multiple pregnancy rate. This is because of the results of serum estradiol levels during the follow up period is delayed , so decision making to withhold the HCG administration is difficult to be taken., but fortunately the hyper-response rate is almost similar. The duration of treatment during the cycle is almost similar to what has been reported [15], they report a mean duration of 13.1 days compared with 14 days in this study.

The number of cycles cancelled because of no response or over response is almost similar to what was reported [16], he reported 23 cycles cancelled in 122 patients studied.

There was no difference in the daily effective dose, number of cancelled cycle, estradiol concentrations and the number of large follicle.

Cumulative pregnancy rates for the same protocols, almost similar 29% compared with 33%.Conventional and low dose step-up protocols yield comparable pregnancy rates [17].

However, the major advantage of the low dose step-up protocol is the achievement of high rate of monofollicular development which is 69%.The prediction of the threshold FSH dose is essential for optimization of ovulation induction using the low dose step-up protocol. Body mass index (BMI) is an important prognostic factor that not only influences cycle cancellation due to no ovarian response, but also threshold FSH dose, White that in women with a BMI greater than 25 kg/m ^{2}, the number of abandoned cycles was higher than that in women of normal weight, (31 versus 11%), the same was found in this study (15 versus 5%).

A model for prediction of FSH threshold using multivariate analysis, and significant predictors for monofollicular development were BMI, presence of clomiphene citrate resistance, initial free insulin like growth factor-1 and initial serum FSH concentrations.

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