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LOW DOSE GONADOTROPIN PROTOCOL FOR OVULATION INDUCTION IN LOW RESOURCE CENTRE

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ABSTRACT

The use of gonadotropins has been advocated for anovulation infertility especially in clomiphene resistant situation. But their use has been limited by the side effects particularly hyper stimulation syndrome as well as high cost/unavailability of the drugs and means of monitoring in the low resource area. The low dose protocol in this prospective study consists of 75IU of human menopausal gonadotropin on day 3, 5 and 7. Seventy three per cent of the patients developed matured Graffian follicle, unifollicle in 56.7% and 70% of them were able to get pregnant over 3 cycles with cumulative pregnancy rate of 32.8% of all the stimulated cycles. This result is favourably compared to outcome in other protocols. There was no incidence of ovarian hyper stimulation syndrome while 3.1% of the patients had twins. Age and duration of infertility appeared to influence the response to gonadotropins ($P < 0.05$) while body mass index and presence of polycystic ovarian disease did not. This low dose protocol will benefit patients in low resource area considering the lower drugs usage with favourable effectiveness, no complication and thereby require little monitoring.

KEYWORDS: Anovulation, Clomiphene Resistant, Gonadotropin, Low Resource Area, Ovulation Induction

INTRODUCTION

Ovulation is the process by which a mature Graffian follicle bursts and releases an egg, which is then picked up by the fallopian tube. This event marks the transition from the follicular phase of the menstrual cycle into the luteal phase.Ovulatory disorders, which hinder or prevent the ovaries from releasing eggs, are one of the most common causes of infertility and account for 30% of women's infertility [1, 2]. Ovulation induction has been one of the most significant advances in the treatment of infertility [3]. Although considered routine today, its origins date back only a relatively short time. The primary goal of ovulation induction is to encourage the recruitment, maturation, and development of only one or two preovulatory follicles. There are various drugs used in ovulation induction which includes clomiphene citrate, tamoxifen, letrozole (aromatase inhibitor) and gonadotropins [2, 4, 5]. Ovulation induction should rightfully be viewed as a safe and reasonable form of treatment for widespread application. However, serious side effects or complications do uncommonly occur especially with the use of gonadotropins.

The use of gonadotropins has expanded tremendously since their introduction into clinical medicine more than 40 years ago. It was initially extracted from human pituitary gland which limited its use due to scarcity of the gland. However its extraction from urine of postmenopausal women made it widely available as human menopausal gonadotropin (HMG) [3].The HMG consists of follicle stimulating hormone (FSH) and Luteinizinghormone (LH). With advances in science, gonadotropin is now available as human recombinant FSH and highly purified urinary FSH. FSH appears necessary in the early phases of the cycle to recruit and select these follicles. For growth and maturation, both FSH and LH are necessary. Women who produce endogenous LH are likely to respond comparably well to either purified FSH or preparations that

contain both LH and FSH [6]. Therefore, an increasing tendency has been for either HMG or purified FSH preparations to be used with comparable expectations.

The initial indication for administering gonadotropins was hypothalamic–pituitary insufficiency in which the patients are amenorrheic with low or normal FSH levels. Other indications include patients with hypothalamic–pituitary dysfunction with normoprolactinemia and normal androgen levels, and those with polycystic ovarian syndrome. Such patients should be given clomiphene citrate first but if they do not conceive after three to six cycles of clomiphene therapy or do not respond with dosages of up to 150 mg per day for 5 days, gonadotropin will be indicated.It is also used in women with unexplained infertility in which it is believed that the combination of gonadotropins with IUI will improve fecundity and perhaps shorten the window of time required to achieve conception [2,].

Different protocols are being used for the administration of gonadotropins for ovulation induction[8,9,10] but should not be above 300IU daily since no additional benefit will be gained[11].The conventional protocol is administration of 75–150 IU/day of HMG or recombinant FSH for 5 -14days [7]. But the setback of all these protocols is the development of ovarian hyper stimulation syndrome (OHSS)and multiple pregnancies [12].OHSS can range from mild to severe, even sometimes be life threatening. Both ultrasound and estradiol assessment are needed for safe and effective monitoring of ovulation induction. Failure to use both greatly increases the risk of OHSS and multiple births [13, 14]. In view of this setback, mild stimulation protocols have increased in recent times [15, 16]. Low-dose gonadotropin therapy has proven effective in inducing unifollicular ovulation, less complications, lower rate of aneuploidy [17] and a more favourable endometrial development [18]. The high cost of gonadotropins viz a viz unavailability/high cost of means to monitor the effect of gonadotropins in low resource areas limit its uses to women in low resource area despite having large number of patients that will benefit from its use. This study is to investigate the effectiveness of a protocol that uses a much lower gonadotropin dosage.

METHODOLOGY

This prospective study was carried out in the gynecological clinic of Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, Osogbo, Osun State in South West of Nigeria from 1st of January 2013 to 31st January, 2015. Thirty patients with anovulatory infertility were recruited for the study. The patients had used clomiphene citrate up to 150mg daily for 5days without evidence of ovulation. Their fallopian tubes were also found to be patent and the male partner had normal semen quality. All of them had ultrasound scan on day 3 of the cycle in order to exclude abnormal ovarian cyst. Informed consent of all the patients used was obtained after thorough counselling. Ethical approval for the study was given by the research and ethics committee of the hospital.

The low dose protocol used involves giving HMG 75 i.u subcutaneously on day 3, 5 and 7. Transvaginal scan with a 7.5-MHz probe was then done from day10 to monitor the follicular growth and endometrial development. Intramuscular injection of HCG 5000 i.u. was given if there is a mature follicle of 18mm and above. The couples were instructed to have intercourse between 24 – 36hrs after the HCG injection. The data obtained was analyzed with Statistical Package for Social Sciences (SPSS) version 20. Chi-square test at P. value<0.05 was considered statistically significant on bivariate analysis.

RESULTS

The age range of recruited patients for this study is 26years to 40years with the mean of 34.67. Sixty six percent

of the patients had primary infertility with most of them having the problem less than 10years as shown in table 1. Features of polycystic ovarian syndrome (PCOS) were found in 73.3% while only 40% were overweight with none obese. Twenty three percent of them had been given gonadotropin in the past from another center using the conventional protocol; the only patient among them withno signs of hyperstimulation couldn't go for another cycle due to financial constraint.

After those patients were subjected to the low dose protocol of this study, 73.4% of them showed development of matured Graffian follicle, mostly on day 12 as in table 2. None of them had more than 2 follicles; unifollicle was obtained in 56.7%. It resulted in pregnancy in 70% of the patients with most of them occurring after the 3rd cycle (46.7%). There was no OHSS in any of the patients while only 2 patients (3.1%) had twins.

In table 2, fourteen patients (46.7%) received the drug over 3 cycles before it resulted in pregnancy while 4 and 6 patients got pregnant after one and two cycles of stimulation respectively. The total stimulated cycles for the 30 patients were 64, out of which there was no response in 6 cycles, single follicle in 51(79.7%) and 2 follicles in 7 (10.9%). The overall pregnancy rate of all the cycles was 32.8%. Table 3 showed the influence of some factors within the patient on the outcome of gonadotropin stimulation. Age and duration of infertility have influence on the response of patients to gonadotropin stimulation ($P < 0.05$) while BMI, type of infertility and presence of PCOS do not.

Table 1: Clinical Features of the Patients

Variables	Number	Percentage
Age		
25 – 30yrs	2	6.7
31 – 35yrs	23	76.7
>36yrs	5	16.7
BMI in kg/m^2		
Normal	18	60
Overweight	12	40
Type of infertility		
Primary	20	66.7
Secondary	10	33.3
Duration of infertility		
1-5yrs	15	50
6- 10yrs	14	46.7
> 10yrs	1	3.3
Presence of PCOS		
Yes	22	73.3
No	8	26.7
Past gonadotropin usage		
Yes with complication	6	20.0
Yes without complication	1	3.33
No	23	76.7

Table 2: Outcome of Ovarian Stimulation

	Number	Percentage
No of Matured follicle produced		
Nil	8	26.7
1	17	56.7
2	5	16.7
Day of matured follicle		
12	14	46.7
13	7	23.3
14	3	10
Does it result in pregnancy?		
Yes	21	70
No	3	10
No of stimulated cycles/patient before pregnancy result		
1	4	13.3
2	6	20
3	14	46.7
No response	6	20

Table 3: Influence of Clinical Features on Gonadotropin Response

Clinical Features	Presence of Follicle			P Value
	Yes	No	Total	
Age group				
25 – 30years	2	0	2	
31 – 36years	19	4	23	0.01
>36years	1	4	5	
Duration of infertility (Years)				
1-5	11	4	15	
6-10	11	3	14	0.002
>10	0	1	1	
Type of infertility				
Primary	15	5	20	
Secondary	7	3	10	0.77
BMI in Kg/m^2				
Normal weight(16-25)	13	5	18	
Overweight(25 -29)	9	3	12	0.87
Evidence of PCOS				
Present	18	4	22	
Absent	4	4	8	0.08

DISCUSSIONS

The aim of this study was to evaluate the effectiveness of this ultra-low dose gonadotropins regimen in order to achieve unifollicular ovulation, reducing cost, minimizing complications and achieving quality pregnancy.The total dose of gonadotropins used in this study (225 I.U) was lower than the entire low dose regimen available in the literatures (> 375 IU) [14, 15, 18].

More than sixty percent of the recruited patients with clomiphene resistant anovulation used in this study had primary infertility with the mean age of 34.67. Majority of them had PCOS as also noted by different studies [2,8].

The ovulation and pregnancy rate in this ultra-low regimen can be favorably compared to other low dose regimen as well as the conventional type [14, 15, 18, 19]. Despite the similar outcome, it is worthy to note that there was no single OHSS in this study. The multiple pregnancy rates of 3.1% are very low despite thatthis study area is known for high incidence of twinning.

It is not surprising that age of patients have influence on the outcome of gonadotropin ovulation induction as shown in this study. It has been found that there is decline in ovulation rate and fecundity after the age of 36years and worse after 40 years of age [20]. The influence of the duration of infertility may be attributed to increasing age of affected women.

This study showed no influence of body weight on the response to gonadotropin usage (p= 0.08), though studies found that body weight affects gonadotropin requirements but not overall outcome of ovulation induction in women with anovulatory polycystic ovarian syndrome [21, 22].Obesity is not common in this environment but there is significant number of overweight women particularly among those with PCOS.

Apart from the minimal drugs used in this study, the use of ultrasonography only to monitor the patients will reduce the cost of gonadotropin ovulation induction. A study had shown that ultrasonography is the mainstay of monitoring in both ovulation induction and IVF without the need for same-day hormone measurements [5]. Hormonal assay is very expensive and not easily available in low resource centres. Since this low dose regimen showed no presence of OHSS, it can be easily administered in low resource centres without fear of patient developing OHSS.

CONCLUSIONS

The use of low gonadotropin doses to induce the maturation of a single follicle seems to be the most realistic therapeutic approach to ovulation induction at present. This low dose protocol used in this study will benefit patients with clomiphene- resistant anovulation in low resource area considering its effectiveness, reduce cost and less complications.

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