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Minimal stimulation protocol: a cheap and effective method of ovulation induction

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نظام التنبيه الأدنى: طريقة رخيصة وفعّالة لإحداث الإباضة.

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الملخص : الهدف: تحديد فعالية وتكلفة نظام "التنبيه الأدنى للمبايض" وهو نظام جديد من العلاج الهرموني لإحداث تنبيه منضبط للمبايض. **الطريقة**: تسجيل معدلات الإباضة ، الحمل ، الإجهاض إلى جانب التكلفة الدوائية في 67 إمرأة تم علاجها بهذا النظام. **النتائج:** نسبة الإباضة كانت 82 % ، نسبة الحمل 2 % ، ونسبة الحمل بأكثر من جنين 7% . وكانت نسبة الإجهاض التلقائي 36 % من إجمالي حالات الحمل. كما بلـغ معدل تكلفة نظام التنبيه الأدنى للمبايض ثلث تكلفة نظام إستخدام هرمون منشط القند ألأنسان. **النتائج:** نظام التنشيط الأدنى للمبايض أرخص بكثير من نظام العلاج بهرمون منشط القند ألأنسا ني وله نفس المفعول ، وهو يتطلب متابعة أقل ولذلك فهو أكثر راحة للمريض. وعليه فإن هذا النظام يستحق الدراسة كعلاج للعقم.

ABSTRACT: ***Objective*** – To determine the effectiveness and cost of Minimal Stimulation Protocol (MSP), a new combination of human menopausal gonadotrophin (hMG) and clomiphene citrate (CC), for controlled ovarian hyperstimulation. ***Method*** – The ovulation rates, pregnancy rates, abortion rates and the cost of medication were assessed in respect of 67 women who underwent MSP. ***Results*** – Ovulation rate in the study group was 82%, pregnancy rate 21% and multiple pregnancies 7%. Spontaneous abortion occurred in 36% of the pregnancies. The average cost of MSP stimulation was one-third of hMG protocol. ***Conclusion*** – MSP protocol, while substantially cheaper than hMG, gives comparable pregnancy rates with less need for monitoring and better patient comfort. These justify further evaluation of its role in the treatment of infertility.

Key words: clomiphene citrate, human menopausal gonadotrophin, minimal stimulation protocol

Ovarian stimulation has been established to be a reasonably effective treatment for non-ovulatory infertility. Clomiphene citrate (CC), a cheap and easy-to-administer drug, was the first one used for ovarian stimulation. For women failing to conceive after four to six cycles of CC, gonadotrophins are the accepted alternative.[1,2] However, the medication and monitoring expenses are higher than those of CC. Cost reduction has been achieved without sacrificing efficacy by using a combination of CC and human menopausal gonadotrophin (hMG).[3,4]

In 1993, Corfman[6] described a novel ovarian stimulation protocol termed *minimal stimulation (MSP).* When used in in-vitro fertilization program (IVF), this protocol gave a clinical pregnancy rate comparable to pure hMG stimulation at lower expense.[6] Although MSP has been reported to be effective for ovulation induction, a widespread search of the literature shows only a few studies using it.[6,7]

Our retrospective study describes the experience with MSP in a non-IVF population over two years and aims to confirm its effectiveness and to ascertain the costs involved. Our results are compared with those for patients treated with a standard hMG ovarian stimulation protocol as described by others.[7]

METHOD

From April 1996 to March 1998, patients presenting to the infertility clinic of Sultan Qaboos University Hospital, Muscat, were offered a stimulation protocol combining CC & hMG. This retrospective study involved 221 minimal stimulation cycles in 67 infertile women.

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The mean age of the treatment group was 28.7 years and the average duration of infertility, 6.1 years. The majority (66%) of the women suffered from primary infertility. The causes of infertility included anovulation (in some cases combined with male factor), tubal diseases or endometriosis and unexplained infertility. Most of them had failed CC therapy before. Intrauterine insemination was performed in women with male factor infertility.

The procedure for MSP was started with administration of 100 mg of CC daily orally from cycle day 3 to 7. A single injection of hMG 150 iu i.m. was given on the 9th cycle-day. Transvaginal ultrasonography was done on the 12th cycle-day to assess follicle size and endometrial thickness. If the leading follicle was seen to be ≥14 mm, its diameter could be expected to increase by 1–2 mm/day, and accordingly, the day of hCG injection was projected. When leading follicle had grown to >18 mm, 10,000 iu hCG was given intramuscularly. If follicle size remained <14 mm, vaginal ultrasound was repeated on the 15th cycle day. If even then there was no follicle ≥ 16 mm, the treatment was considered failed.

Criteria for ovulation induction failure were ultrasonic finding of a leading follicle <19mm and/or an endometrial thickness <8mm. Criterion for treatment failure was inability to become pregnant during 4 courses of treatment. A clinical pregnancy was defined as visualization of the gestational sac by transvaginal ultrasound performed 4 weeks after hCG administration. We follow the criteria published by Lu et al.[7]

RESULTS

A total of 67 women who completed 221 ovarian stimulation cycles were included in the analysis. Ovulation occurred in 82% of treatment cycles and each patient received 10,000 i.u. hCG. The treatment was cancelled in 18% of cycles mainly because of inadequate follicular growth. Only ovulatory dysfunction was found in 63% of the patients. The other causes for infertility included male factor, tubal diseases, endometriosis and unexplained infertility (table 1).

In the study group, 21% patients (14 out of 67) became pregnant. Table 2 summarizes the outcome of these pregnancies. Abortion rate was high at 36%, and all except one occurred before 10 weeks gestation. One woman aborted triplets at 20 weeks gestation. There were 9 successful pregnancies, resulting in live babies.

Table 3 shows the number of pregnancies in each cycle. Maximum pregnancy rate was noticed in the first cycle. Although the original protocol advocates 4 cycles of treatment, 17% of our patients received more than 4 cycles and 14% of our pregnancies occurred during the 5th and 6th cycles.

TABLE 1

Characteristics of 67 women treated with MSP

	No.	%
Ovulatory dysfunction	42	63
Male factor	12	18
Tubal diseases	10	15
Endometriosis	9	13
Unexplained	8	12

N.B. The total number is > 100% because some of the patients appear more than once due to combined factors of infertility.

TABLE 2

Outcome of 14 pregnancies achieved with MSP

	No	**%**
Completed pregnancy	9	64
Abortion rate	5	36
Total	14	100
Singleton pregnancy	13	93
Multiple pregnancy	1	7
Total	14	100

TABLE 3

Number of pregnancies in each treatment cycle

Cycle	Pregnancy	%
1st	5	36
2nd	4	29
3rd	0	0
4th	3	21

THE COST FACTOR

SQU Hospital pharmacy charges were (approximately) Rials Omani (RO) 2.200 (US $5.70) for 5 days' treatment with CC at 100 mg per day, RO 3.200

($8.30) for 150 i.u. hMG, and RO 3 ($7.80) for 10,000 i.u. hCG. Thus, the average medication expenses for MSP is RO 8.400 ($22), one-third of the RO 25.500 ($66) required for hMG stimulation. Also to be noted is MSP's lower monitoring requirements: whereas monitoring of hMG cycle usually requires several transvaginal scans and serum Estradiol estimations, MSP needs only one, or at the most, two transvaginal scans. (Due to the variability of the number of serum estradiol estimations in monitoring of HMG-only protocol, and the difficulty in calculating the cost of transvaginal ultrasound examinations, the exact savings on monitoring requirements could not be worked out.)

DISCUSSION

Our study shows that MSP may be used for achieving late follicular growth. Patients who fail to ovulate or do not conceive with CC therapy may benefit from this CC-cum-hMG regime before hMG-alone therapy is administered. Majority of the patients in this study had previous unsuccessful CC cycles. MSP was offered as a 'next step' after CC failure. Its reduced cost and monitoring were attractive to the patients.

Single leading follicle of size >18 mm was considered as ovulatory in our study compared to 2 or more follicles of 20mm size in original MSP.[5-7] It is our practice to cancel the treatment cycle in the presence of a thin endometrium.[8,9] Endometrial thickness ≥ 8mm occurred in 87% of ovulating cycles. Only 30% of non-ovulating cycles had endometrial thickness > 8mm, and none of the patients in this group conceived, thus confirming the results achieved by the other authors.[10] Ovulation and pregnancy rates were comparable to hMG stimulation reported by Lu.[7] However, the abortion rate of 36% in our group was significantly higher than in the MSP group reported by the above author. The reason for this variation is not clear. The treatment cycle were cancelled in 18% due to poor follicular growth compared to the cancellation rate of 26% in the MSP and 14% in the hMG protocol reported by Corfman[6].

Although the original protocol suggests a maximum of 4 cycles[5-7], 17% of our patients received up to 6 cycles and 14% of pregnancies occurred in this group. Combined infertility factors were the reason for extending the therapy.

CONCLUSION

From the above, MSP appears to be an effective protocol for controlled ovarian stimulation in infertile women. It is easy to administer, requires less intense monitoring, fewer medications, and is cheaper. On drug costs alone, MSP protocol is 1/3rd cheaper than hMG protocol. In addition to this are the savings on monitoring. These factors make minimal stimulation protocol a reasonable therapeutic option to a pure hMG treatment.

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