ROLE OF SEQUENTIAL CLOMIPHENE CITRATE AND HUMAN MENOPAUSAL GONADOTROPIN IN INTRA UTERINE INSEMINATION PROGRAMME

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SUMMARY

This study evaluates the different protocols of ovarian stimulation such as (1) only clomiphene citrate, (2) only gonadotropins and (3) sequential clomiphene citrate and gonadtropins. A total of 2402 cases of infertility reported to Manipal Assisted Reproduction Centre over a period of 2 years (1992 - 94) of which 921 women with unexplained infertility were recruited for IUI with washed sperms. Per cycle fecundity was better with the sequential clomiphene and gonadotropin protocol (0.05) when compared to those with only clomiphene (0.02) or only gonadtropin (0.04) and all the three protocols put together (0.03). By increasing the number of attempts the fecundity was not increased significantly. The corrected pregnancy rate was better with sequential clomiphene + hMG protocol (17.28%) when compared to the other two. Hence in our opinion ovarian stimulation with sequential CC, + hMG results in increased fecundity (double that of CC alone) and similar fecundity of hMG alone protocol thereby reducing the requirement of hMG and its accompanied problems.

INTRODUCTION

Intra uterine insemination (IUI) has been performed for some years now. In the past few years there has been increased interest in ovarian stimulation with gonadotropins, prior to IUI (Dodson and Heney, 1991 and Kemmann et al 1987). This study evaluates the different protocols of ovarian stimulation such as (1) only clomiphene

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citrate, (2) only gonadotropins and (3) sequential clomiphene citrate and gonadtropins. Correction of subtle and unpredictable ovulatory dysfunction is thought to be the rationale behind induction of ovulation. Furthermore controlled superovulation provides enhanced opprtunity for fertilisation with IUI of washed sperms.

MATERIAL AND METHODS

A total of 2402 cases of infertility reported to Manipal Assisted Reproduction Centre over a period of 2 years (1992 - 94) of which 921 women with unexplained infertility were recruited for IUI with prior ovarian stimulation. These women were randomly allotted to three groups as follows: Group (1) Only clomiphene citrate (CC): CC 50 mg 1 od from day 2 to day 6, Group (2) Sequential clomiphene citrate and gonadtropin (hMG): CC 50 mg 1 od from day 2 to day 6 followed by injection hMG 1 ampule (75 IU FSH + 75 IU LH) per day from day 7 to day 10 and Group (3) Only gonadtropins: 2 ampules of hMG per day from day 5 and later tailored according to the follicular response. All the cases were monitored by transvaginal sonography for follicular dynamics. When the leading follicle was more than 18 mm, hCG was given and 36 hours after the injection of hCG, IUI was performed with washed sperms. Sperm preparation was done as follows: The samples were centrifuged twice with nutrient medium F-10 Ham (ICN Biomedicals USA) supplimented with bovine serum albumin (Sigma Chemical Co USA). The resulting pellet was overlayed with 0.5 ml of the medium and incubated for 1 hour at 37 XC (swim up technique).

OBSERVATIONS

A total of 921 patients with unexplained infertility were recruited for IUI with ovarian stimulation. The mean age of the patients was 30 years and the duration of infertility ranged between 2 to 12 years.

Per cycle fecundity by diagnostic entity:

The results of controlled ovarian hyperstimulation of IUI in cases of unexplained infertility, described as pregnancies per cycle initiated, are presented in

Table I
PER CYCLE FECUNDITY BY DIAGNOSTIC ENTITY

Protocol	No of women	No of cycles	No of pregnancies	Pregnancies/ cycle	Fecundity
Only CC	617	1755	45	45/1775	0.02
Sequential CC + hMG	225	529	28	28/529	0.05
Only hMG	79	90	4	4/90	0.04
Total	921	2374	77	77/2374	0.03

Table I. Per cycle fecundity was better with the sequential clomiphene and gonadotropin protocol when compared to those with only clomiphene or only gonadotropin and all the three protocols put together.

Per cycle fecundity by cycle attempt:

The crude cycle fecundity for all attempts was 0.03 as shown in Table I. However Table II shows that by increasing the number of attempts the fecundity was not increased significantly. In fact the fecundity was better in the first cycle attempted, in all the protocols more so in that with sequential clomiphene and hMG.

Corrected pregnancy rate:

Couples who had at least 3 attempts or conceived within 3 attempts were considered to calculate the pregnancy rate. The corrected pregnancy rate was better with sequential clomiphene + hMG protocol when compared to the other two (Table III).

Table II
PER CYCLE FECUNDITY BY CYCLE ATTEMPT

Protocol	Cycle No	Pregnancy/Cycle	Fecundity
Only CC	1	21/359	0.05
	2	5/125	0.04
	3/more	19/1271	0.01
Sequential	1	17/149	0.11
CC + hMG	2	7/58	0.12
	3/more	4/322	0.01
Only hMG	1	2/16	0.12
	2	2/21	0.09

Table III
CORRECTED PREGNANCY RATE

Protocol	No of women	No of pregnancies	Pregnancy rate
Only CC	305	45	14.75%
Sequential	162	28	17.28%
Only hMG	46	4	08.69%

DISCUSSION

Ovarian stimulation followed by IUI has been used as specific as well as emperic treatment in cases of subfertility. In this study 3 types of protocols were used for ovarian stimulation in cases of unexplained infertility. Several authors (Cruz et al, 1986 and Serhal et al, 1988) have suggested that IUI in superovulated women increased the fecundity. Cruz et al (1986) in their prospective randomised cross over study of 49 couples, reported that the fecundity was 0.07. Serhal et al (1988) compared superovulation alone and controlled ovarian hyperstimulation coupled with IUI. Their study revealed that addition of IUI was associated with an increase in the per cycle fecundity from 0.06 with superovulation alone to 0.26 with controlled ovarian stimulation coupled with IUI. Deaton et al (1989) in a randomised prospective trial compared CC + IUI with well timed intercourse in couples with unexplained infertility and found that the fecundity was 0.08 with CC + IUI when compared to that with well timed intercourse (0.03). The per cycle fecundity in the present study was comparable to those found by other workers (Table IV)

The cycle fecundity decreases as the number of cycles increase as mentioned by Remohi et al (1989). In their study of 489 cycles of controlled ovarian hyperstimulation and IUI the cycle fecundity for the first 4 cycles was 0.07. The cycle fecundity for the 5th through 11th cycle, was 0.03. Further 94% of the pregnancies occured in the first 4 cycles. In the present study also the fecundity was better in initial cycles in all the protocols and there was no further improvement by increasing the attempts (Table II).

The need for frequent injections, strict monitoring, possibility of multiple gestations and above all the higher cost of gonadotropins when compared to clomiphene, prevent many clinicians from using hMG for ovarian stimulation. The sequential CC + hMG protocol used in the present study overcomes these problems. Dickey et al (1993) showed in a

Table IV
PER CYCLE FECUNDITY IN UNEXPLAINED INFERTILITY - A COMPARISON

Only CC cycles	Fecundity	Only hMG cycles	Fecundity
Bolton et al (1989)	0.03	Hevath et al (1989)	0.03
Hewitt et al (1988)	0.05	Cruz et al (1986)	0.07
Present study	0.02	Present study	0.04

retrospective study that the per cycle fecundity was 0.11 with CC alone when compared to that with sequential CC + hMG (0.22 double that of CC alone) and hMG alone (0.18 - almost equal to sequential CC + hMG). The present study showed similar results. Hence we conclude that ovarian stimulation with sequential CC + hMG results in increased fecundity (double that of CC alone) and similar fecundity of hMG alone protocol thereby reducing the requirement of hMG and its accompanied probelms.

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