

Study of Cycle Specific Factors in Successful Cases of I.U.I. With Cryopreserved Donor Semen

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Summary

A retrospective study was done of 107 cycles of IUI in 61 women who conceived after insemination with cryopreserved donor semen. The dose of clomiphene citrate, number of pre-ovulatory follicles and the diameter of dominant follicle at the time of giving HCG to trigger ovulation was studied in these cycles and comparison was made between the cycles in which the women conceived and in the earlier cycles in which they did not conceive. Simultaneously, the effect of Clomiphene Citrate on number of follicles and its effect on chances of conception was also studied. There was greater number of pre-ovulatory follicles in the cycle in which the women conceived compared to the earlier cycles. The diameter of dominant follicle was not significantly different in conception and nonconception cycle, neither was the dose of clomiphene citrate used. There was no uniform change in follicular number or diameter with change in dose of CC. It is concluded that though the chances of conception are more with more number of follicles yet use of higher dose of clomiphene citrate does not lead to increase in number of pre-ovulatory follicles or in the chance of conception.

Introduction

There are various factors which can affect the success of any infertility therapy including donor insemination. The age of woman, duration of infertility, tubo-peritoneal status, endocrinological abnormalities and other causes of unexplained infertility are few of those factors which remain static between cycles over a short duration of time. The factors which change with every cycle are the amount of ovarian stimulation given, the number of pre-ovulatory follicles, the diameter of dominant follicle at which HCG is given to trigger ovulation and the quality of semen used for the particular procedure.

The chances of conception are increased with increased number of pre-ovulatory follicles and proper timing of insemination (Edwards & Brody, 1995).

Clomiphene citrate is given during donor insemination as it ensures follicular development and increases the number of follicles (Wong et al, 1989). In most of the ART procedures the timing of insemination is based on giving HCG as a surrogate LH surge after the dominant follicle reaches a particular diameter. The follicular maturity is said to have occurred when the dominant follicle reaches 18 to 24mm in diameter.

If we study the conception and nonconception cycles in the group of women who conceive after intra uterine insemination (IUI) with donor semen then the effect of age, duration of infertility, tubal status, cervical factor, male infertility status and other causes of unexplained infertility can be negated as these factors do not change in a particular woman over a short period of time. Thus, the study of these cycles gives us an opportunity to see the effect of follicular number,

follicular diameter and CC dose on chances of pregnancy.

This was a retrospective study of women who conceived after IUI with cryopreserved donor semen to find out the difference in stimulation given, number of pre-ovulatory follicles before giving HCG and the diameter of dominant follicle at the time of giving HCG in the cycle in which these women conceived and earlier cycles in these women in which they did not conceive. The only other variable was the cryopreserved semen sample but its effect was controlled by insemination with a critical level of motile sperm count (5million/ml).

Material and Methods

Three hundred & thirty patients were accepted for donor insemination with cryopreserved semen during the period of Dec., 1997 to April, 2000 at Srijan, Centre for Assisted Human Reproduction, Patna. Detailed history was taken. VDRL of both partners was done. Blood grouping and Rh typing of recipient couple was done. The only prerequisite was at least one patent tube on H.S.G. Other investigations like diagnostic laparoscopy and serum prolactin were done if required. Follicular stimulation was done with CC 50 to 150 mg from 2nd to 6th day of the cycle. Follicular monitoring was started from 10th day of the cycle using 5 MHz transvaginal probe and 5,000 I.U. of H.C.G. was given I.M. when the size of the leading follicle reached 18-24mm. Written consent was taken from the couple. IUI was done only once in each cycle with Makler cannula. 0.5 ml of cryopreserved semen was used for intra-uterine insemination which was done about 36 hours after HCG injection. Cryopreserved semen was used after checking the number of motile spermatozoa, the cut-off point being at least 5 million motile sperm/ml. IUI was done in lithotomy position without using any sedation or anaesthesia. Patients were asked to rest for half an hour on the table after the procedure and then allowed to return home. Ampicillin 250mg was given orally 4 times a day for 5 days. Luteal support with progesterone was

given in selected cases. No limitation of activity was advised after the patients were discharged. Follow up was done with β HCG 14 days after insemination or with vaginal sonography 25 days post insemination.

Result

Three hundred thirty patients taken into programme of donor insemination with cryopreserved semen during the period of Dec, 1997 to April, 2000 underwent 735 cycles of IUI resulting in 61 pregnancies. The mean age of patients who conceived was 26.45 (\pm 0.44) years. The mean duration of infertility was 8.53 (\pm 0.53) years. A total of 107 cycles were done in these 61 patients with a mean of 1.75 (\pm 0.13) cycles per patient. Thirty four women conceived in the first cycle of treatment and 27 patients needed more than one cycle to conceive in whom total 46 cycles were done as repeat procedure.

There was one follicle in 23.33% of the patients in the conception cycle while 35% had two and 41.66% had three or more follicles. In the earlier cycles in these patients, 50% of the cycles were monofollicular and 20% of the cycles had three or more follicles. (Table-I).

Table I
Frequency Distribution of Patients according to No. of Follicles.

Number of Follicles	Conception Cycle	Non Conception Cycle
1	14 (23.33%)	20 (50%)
2	21 (35%)	12 (30%)
3	14 (23.33%)	4 (10%)
>/= 4	11 (18.33%)	4 (10%)

On studying the frequency distribution of the diameter of dominant follicle it was noticed that the diameter of most of the follicles at the time of giving HCG was 18 to 23 mm in both conception and non-conception cycles. (Table II).

Table III
Comparison of Means between Conception and Nonconception cycles

	Conception Cycle	Non conception Cycle	Difference	t-value	p-value
Mean diameter of Dominant Follicle (mm.)	20.62 (\pm 0.47)	20.28 (\pm 0.4)	0.34	0.52	0.6
Mean No. of Follicles	2.45 (\pm 0.15)	1.78 (\pm 0.15)	0.67	2.95	0.003
Mean dose of clomiphene citrate (50 mg tab/day)	1.58 (\pm 0.08)	1.47 (\pm 0.09)	0.11	0.85	0.3

Table II
Frequency Distribution of Patients According to Diameter of Dominant Follicle

Diameter of Dominant Follicles	Conception Cycle	Non Conception Cycle
</= 17mm	6 (10%)	3 (7.14%)
18-20mm	30 (50%)	25 (59.52%)
21-23mm	15 (25%)	7 (16.66%)
24-26mm	4 (6.77%)	7 (16.66%)
>/= 27mm	4 (6.77%)	0

In the conception cycle the mean dose of CC (50mg tab per day) was 1.58 (\pm 0.08) and the mean number of preovulatory follicles at time of giving ovulatory dose of HCG was 2.45 (\pm 0.15). The mean diameter of dominant follicle at this time was 20.62 (\pm 0.47)mm (Table III).

The mean dose of CC was 1.47 (\pm 0.09) tab per day in the earlier non-conception cycles. The mean number of follicles in these earlier cycles was 1.78 (\pm 0.15) and the mean diameter of dominant follicle was 20.28 (\pm 0.40) mm. (Table III).

The correlation between CC and number of preovulatory follicles was positive in non-conception cycles while it was negative in conception cycles but the value was significant only for the nonconception cycles i.e. the number of follicles were significantly increased on increasing the dose of CC in nonconception cycle while it was not so in the ultimate conception cycle (Table IV).

Table IV
Correlation Between Dose of Clomiphene and Number of Follicles

	Correlation Coefficient in conception cycle		Correlation Coefficient in non-conception cycle	
	r	p-value	r	p-value
Clomiphene Citrate (50mg tab/day) and Number of follicles	-0.07	(0.6)	0.26	(0.09)

Table V
Distribution of patients according to effect of clomiphene dose on diameter of follicles in conception cycle compared to non-conception cycles.

Follicular diameter in conception cycle compared to earlier cycles	Dose of Clomiphene in Conception Cycle compared to earlier cycles		
	Equal	More	Less
More	5	2	0
Less	7	2	1
Same	5	2	1
Variable	1	0	0
Total	18	6	2

In the 26 patients who needed more than one cycle to conceive, 18 had received the same dose of CC in conception and earlier nonconception cycles, 6 conceived with higher dose and 2 conceived with lower dose (Table V).

In 18 women who received equal stimulation, the diameter of follicle at the time of giving HCG in conception cycle was more in 5, equal in 5 and less in 7 patients compared to earlier nonconception cycles (Table V).

In 6 patients who received more stimulation in the conception cycle compared to earlier cycles, the diameter of dominant follicle at the time of giving HCG in conception cycle was more in 2, equal in 2 and less in 2 patients as compared to the diameter in earlier nonconception cycles. (Table V).

On studying the relationship of change in dose of CC on the number of preovulatory follicles in the 26 women who needed more than one cycle to conceive, we find that in the 18 patients who received the same dose of stimulation, the number of follicles in conception cycle was more in 10 patients and equal in 6 patients compared to earlier cycles. (Table VI).

Among 6 patients who received greater dose of CC, one patient had more follicles in conception cycle while 3 had equal and 1 had fewer number of follicles compared to earlier nonconception cycles. (Table VI).

Table VI

Distribution of patients according to effect of clomiphene dose on number of follicles in conception cycle compared to non-conception cycles

Number of Follicles in conception cycle compared to earlier cycles	Dose of Clomiphene in Conception Cycle compared to earlier cycles		
	Equal	More	Less
More	10	1	1
Less	0	1	1
Same	6	3	0
Variable	2	1	0
Total	18	6	2

Table VII

Effect of Ovarian stimulation on follicular diameter and number of follicles in conception cycle compared to non-conception cycles

Clomiphene dose in conception cycle compared to earlier non conception cycles	Follicular Diameter	No. of Follicles	No. of Patients
Equal Dose	Same	Same	2
	Same	Variable	1
	Variable	Variable	1
	Same	More	2
	Increased	Same	2
	Increased	More	3
	Decreased	Same	3
Increased dose	Decreased	More	4
	Same	Same	1
	Same	Variable	1
	Same	More	1
	Increased	More	1
	Increased	Same	1
	Decreased	Less	1
Decreased dose	Decreased	Less	1
	Same	More	1

When the change in both follicular diameter and follicular number was considered simultaneously according to change in dose of CC, in only 1 out of 8 patients who had received more stimulation, both the diameter and number of follicles had increased. In 18 patients who had received similar amount of CC in conception cycle compared to earlier cycles, 3 had increased diameter and number of follicles in the conception cycle. (Table VII).

Discussion

In numerous studies of IUI in homologus (Nuojuua-Huttunen et al, 1999) and donor insemination (Pittrof et al, 1996) it was shown that pregnancy was related significantly to number of follicles. In our study too there were significantly more follicles in conception cycle. (Table I & III).

In IUI with homologus semen, in 381 cycles in 215 couples, it was shown that recruitment of at least 2 mature follicles was critical for the procedure to be a success (Plosker et al, 1994). In this study too, in conception cycles, 76.66% had more than one follicle, as against 50% in nonconception cycles (Table II).

In a study of controlled hyperstimulation with HMG, (Silverberg et al; 1991) it was shown that percentage of follicles that ovulated after giving HMG increase in follicular size from 14 to 20mm. Though HMG stimulation was not used in this study, there was not significant difference in follicular diameter in conception and nonconception cycles. (Table III).

In a study of IVF (Ectors et al, 1997) it was shown that follicular size is positively related to the oocyte ability to fertilise. The best results were obtained in cases

where the follicle measured 16 to 23mm in diameter. In our study HCG was given only when dominant follicle was at least 16mm so the effect of smaller than 16mm diameter of follicles on conception could not be studied. The response of follicles to the dose of CC on number and diameter of follicles was unpredictable in our study. Although there was significant positive correlation between dose of CC on number of follicles in nonconception cycle, it was actually negatively correlated in conception cycle though this was insignificant (Table IV).

In patients undergoing repeat procedures with equal stimulation, the follicular size was same in 27.77% (n=5), more in 27.77% (n=5) and less in 38.88% (n=7) in the conception cycles. In the 6 patients who had received higher dose of CC in conception cycle, 2 patients had more, 2 had less and 2 had similar diameter of follicles in conception cycle compared to the earlier cycles. (Table V) Thus by increasing the dose or selecting the follicular size at which HCG is given, an increased chance of pregnancy could not be predicted over the range of 16-24mm. In our study, pregnancy occurred in 4 patients when HCG was given with follicular diameter was more than 24mm and even upto 37mm. So it is not always prudent to cancel the cycle in these cases.

The effect of change in CC dose to cause a change in follicular number so as to increase the chances of pregnancy was also not uniform. In 6 patients who had received higher dose of CC in conception cycle compared to earlier cycles, only 16.66% (n=1) had more number of follicles in conception cycle compared to nonconception cycle while 49.99% (n=3) had same number of follicles in the conception cycles compared to earlier cycles. Even with equal stimulation in conception and nonconception cycles in 18 women who conceived, there were more follicles in 55.55% (n=10) of women in conception cycles than in the earlier cycles. (Table VI).

Conclusion

Though chances of conception are more with increasing number of pre-ovulatory follicles, this can not be ensured by giving CC in higher dose. CC is known to stimulate and thus increase the number of follicles but the response is unpredictable and increasing its dose does not always lead to increase in number of follicles or increase in pregnancy rate. A better type of stimulation such as HMG or FSH may be needed (Matoras et al, 1996). Similarly, increase in chances of pregnancy is not related whether HCG is given at 18 to 20, 21 to 23 or 24 to 26mm diameter of the dominant follicle.

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