

Evaluation of treatment in unexplained infertility

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Summary : Seventy four couples having unexplained infertility were enrolled and treated by giving clomiphene Citrate (CC) followed by intrauterine insemination (IUI) with husband's prepared semen. Upto a maximum of six cycles of IUI were offered. Pregnancy rate in this group was found to be 20.1%. Out of 16 pregnancies achieved, 3 were spontaneous conceptions; 6 conceptions followed CC administration and 7 conceptions were the result of CC and IUI.

Introduction

Infertility is a global problem. Approximately 10-15% of couples fail to conceive after at least one year of marriage during which no contraception is used (Guttamacher 1956). Despite improved diagnostic techniques, in most fertility clinics there remains a residue of 24% to 28% of couples in whom no cause of infertility can be found (Templeton et al 1982, Hull et al 1985). Such couples are labelled as having "Unexplained Infertility". By definition the cause of unexplained infertility is not known, but results of various studies suggest that unexplained infertility may have resulted due to multifactorial causes like abnormal sperm parameters, endocrine abnormalities (Haxton et al 1987) and occult infection (Friberg 1980) etc. Such patients are given a host of empirical treatments that achieve a pregnancy rate no better than spontaneous pregnancy rate of untreated couples. Studies using life table analysis (Collins et al 1983, Basnea et al 1985), have shown that many couples with unexplained infertility will conceive without treatment with passage of time. This observation suggests that a relative rather than absolute defect may be responsible for infertility in many of these couples.

Earlier studies from our Institute investigating the causes of infertility had shown almost one fourth of couples as having unexplained infertility. This study was carried out to evaluate the treatment with intrauterine insemination (IUI) using husband's prepared sperm in clomiphene citrate (CC) stimulated cycles in couples with unexplained infertility

Material and Methods

Patients attending the infertility clinic in Gynaec. department of Nehru Hospital, PGIMER were interviewed and screened for the causes of infertility. A total of 1277 couples attended the infertility clinic of our institute between April 1992 and June 1995. A detailed history and examination was carried out in both partners. The couples were thoroughly investigated to arrive at the diagnosis. The investigations of the female partner included complete haemogram, urine analysis, X-ray chest and premenstrual endometrial biopsy to detect ovulation and rule out endometrial tuberculosis. Tubal factor was evaluated by hysterosalpingogram and diagnostic laparoscopy. Cervical mucus scoring and post coital test was done to rule out the cervical factor of infertility and test for antisperm antibodies was done for immunological causes of infertility if PCT was repeatedly poor. The male partner was asked to obtain detailed semen analysis comprising assessment of number of spermatozoa per ml, motility of the spermatozoa and presence of leucocytes to look for accessory gland infection. After detailed investigations attempt was made to ascertain cause of infertility and patients who did not demonstrate any abnormality in any of the tests were booked as cases of unexplained infertility.

Protocol

Patients with unexplained infertility were given clomiphene citrate 100 mg daily from day 5 of the periods for five days. Ovulation was monitored by transvaginal ultrasound. When dominant follicle measured 18-20 mm

Table I
Causal Analysis of Infertility

	No.	%
Total couples interviewed	1277	
couples investigated	945	
Female causes	602	(63.7)
Male causes	229	(24.2)
Unexplained infertility	114	(12.1)

Table II
Unexplained Infertility

	No.	%
Couples booked	83	
Dropouts	9	
Analysed	74	
Number of pregnancies	16	(21.6)
After IUI	7	
After CC	6	
Spontaneous	3	

Table III
IUI in Unexplained Infertility

	No.	%
Patients offered IUI	74	
Number of cycles covered	173	
Number of procedures	266	
Number of pregnancies	7	(9.5)
Preg. rate/ cycle		(4%)

in diameter inj. HCG- with husband's prepared semen 36-40 hours after injection of HCG.

Semen preparation for IUI was done by sperm swim up technique. Fresh ejaculate collected by masturbation in a sterile container was allowed to liquify and incubated for 30 minutes. The semen was then overlaid with two volumes of Bigger whitting whittington (BWW) medium containing bovine serum albumin in a sterile test tube which was placed at an angle of 30° for one hour to

allow the motile spermatozoa to swim up into the culture medium. The supernatant was then transferred to another sterile tube and centrifuged for five minutes. The final pellet was resuspended in 0.3 ml of the medium and the sample was used for intrauterine insemination. For intrauterine insemination a pediatric feeding tube No. 6 was used threaded over 18 G needle attached to 2 C.C. syringe. After visualising the cervix the pediatric feeding tube was introduced in the uterine cavity and contents of the syringe containing prepared semen were injected in the uterine cavity and patient was made to lie down for 15 minutes with her buttocks elevated by a pillow. IUI was done upto 6 cycles.

Pregnancy was confirmed by pregnancy test and ultrasound whenever periods were overdue by one week.

Statistics - Life table analysis was performed on the data.

Results : Of the total of 1277 couples, 945 could be investigated completely to reach a diagnosis. Others could not be worked up completely because of non-compliance or due to occurrence of pregnancy. The causal distribution has been shown in table 1. Male factor was found to be responsible in 229 patients (24.2%), female factor in 602 (63.7%) and in 114 no cause could be found. These 12% of the patients had unexplained infertility.

A total of 83 patients were booked as unexplained infertility in whom no cause could be found. Nine patients dropped out after booking. Incidence of pregnancy in this group was 21.6% (16 pregnancies). Seven pregnancies were after IUI; 6 after clomiphene (they had not come for IUI after taking clomiphene) and 3 patients in this group conceived spontaneously (Table 2). Details of IUI are shown in table 3. Seventy four patients underwent IUI in 173 cycles resulting in 7 pregnancies (4% / cycle). Some of them had IUI in more than one cycle. Life table analysis of pregnancies for all these patients is shown in table 4. Five of these pregnancies occurred in the first two cycles; the other two occurred in third and fourth cycle each. Conditional and cumulative probability of pregnancy per cycle was also calculated.

Table IV
Life table Analysis for Patients undergoing IUI

Cycle	No. of Patients	Conceptions	Withdrawals	Probability of conception/cycle	Cumulative probability
1	27	3	6	.11	.11
2	18	2	5	.11	.22
3	11	1	1	.09	.31
4	9	1	-	.11	.42
5	8	-	7	-	.42
6	1	-	1	-	.42

Discussion

Patients with unexplained infertility present the most challenging situation for treatment. Unexplained infertility should perhaps be more properly designated as subfertility because a high proportion of couples will conceive with passage of time without therapy. In the present study 4% of the couples had spontaneous conception after enrolment without any treatment. Six pregnancies occurred with clomiphene citrate (8.1%). A double blind trial of evaluation of treatment with clomiphene citrate (CC) and human chorionic gonadotropin in cases of unexplained infertility concluded that CC is useful in treating unexplained infertility and is a reasonable initial therapy. (Fisch et al 1989). The mechanism may be that induction of multiple ovulation with CC overcomes a relative defect in fertilization or implantation. IUI has been used in the treatment of unexplained infertility for many years (Allen et al 1985). The efficacy has been evaluated in various studies and results have been found to be poor when IUI was used in unstimulated cycles (Kossakowski et al 1993, Serhal et al 1988). The experience from literature indicates that the combined use of controlled ovarian hyperstimulation using gonadotrophins and IUI may show a potentiation of effects (Dobson et al 1991). The mechanism postulated is an increase in number of male - female gametes at the site of fertilization. In our study IUI was used in CC stimulated cycles and only 7 pregnancies resulted. To know the optimal number of IUI cycle attempts before proceeding to other assisted reproductive technologies, life table analyses have been used. In our study out of the 7 pregnancies achieved with IUI, 5 occurred in the first two cycles. Similar

experience has been reported in previous studies (Lalich et al 1988, Friedman et al 1991). The mechanism may be that induction of multiple ovulation with CC overcomes a relative defect in fertilization or implantation. IUI has been used in the treatment of unexplained infertility for many years (Allen et al 1985). The efficacy has been evaluated in various studies and results have been found to be poor when IUI was used in unstimulated cycles (Kossakowski et al 1993, Serhal et al 1988). The experience from literature indicates that the combined use of controlled ovarian hyperstimulation using gonadotrophins and IUI may show a potentiation of effects (Dodson et al 1991). The mechanism postulated is an increase in number of male - female gametes at the site of fertilisation. In our study IUI was used in CC stimulated cycles and only 7 pregnancies resulted. To know the optimal number of IUI cycle attempts before proceeding to other assisted reproductive technologies life table analyses have been used. In our study out of the 7 pregnancies achieved with IUI 5 occurred in the first two cycles. Similar experience has been reported in previous studies (Lalich et al 1988, Friedman et al 1991).

Conclusion

Intrauterine insemination in cycles with controlled ovarian hyperstimulation using human gonadotrophins is of benefit in patients of unexplained infertility.

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