SUPEROVULATION-INTRAUTERINE INSEMINATION: AN ADDITIONAL TOOL IN THE TREATMENT OF INFERTILITY

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ABSTRACT

The next step in the treatment of infertility after ovulation induction is usually in vitro fertilisation (IVF) or some other sophisticated and expensive assisted reproductive technique. This study looks at the method of superovulation-intrauterine insemination (SO-IUI) as an alternative before IVF in the treatment of infertility.

The first 7 months of this programme were reviewed. There was a clinical pregnancy rate of 20.5% per patient. Ninety-six percent of the pregnancies occurred in the first two cycles. The cycle-cancellation rate was 5.1%. The highest success was in couples with ovulatory disorders, endometriosis and cervical factor infertility. The study suggested that SO-IUI is a cheaper and effective additional tool in the treatment of some infertility disorders before proceeding to IVF or other sophisticated techniques.

Keywords: *infertility treatment, superovulation and intrauterine insemination, cheaper, effective.*

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INTRODUCTION

In vitro-Fertilisation (IVF) was originally developed to treat infertility in women with irreparably damaged fallopian tubes[1]. Early success with this treatment encouraged many clinicians to apply IVF to infertile couples who had normal adnexal structures and had other causes of infertility such as endometriosis, cervical factor infertility, idiopathic infertility and male infertility[2]. The theoretical basis for this was the hope that cycle fecundity could be improved by increasing the number of oocytes per cycle as well as by eliminating any subtle defects of tubal function present. Unfortunately, IVF incurred not only high costs, it was also invasive and extremely stressful to the infertile couple.

The combination of superovulation and intrauterine insemination has the potential to maximise conception by increasing the number of mature oocytes released in a given treatment cycle and by inseminating a concentrated fraction of motile sperms, thereby increasing the density of male and female gametes in the fallopian tubes. In addition, the patient is not subjected to invasive oocyte retrievals. Thus, we looked into this simplified method of infertility treatment as an alternative and cheaper option for patients before going on to more sophisticated assisted reproductive techniques.

MATERIALS AND METHODS

The Department of Reproductive Medicine first started this programme of superovulation-intrauterine insemination in July 1993. One hundred and twenty-two patients underwent the programme between July 1993 and January 1994 and their records were reviewed retrospectively.

Infertility evaluation included a medical history, physical examination of the woman, at least one semen analysis (within 6 months of registration for the programme), documentation of ovulation by mid-luteal serum progesterone concentration of >30 nmol/ml and diagnostic laparoscopy and hysteroscopy. Additional tests such as postcoital test, sperm-cervical mucus contact (SCMC) test and mixed agglutination reaction (MAR) tests were also done.

Infertility factors were defined as follows (some couples may have more than one infertility factor):

* Endometriosis – documented by visualisation at laparoscopy or laparotomy of typical active implants of endometriosis. Extent of endometriosis was classified according to The American Fertility Society revised classification of Endometriosis[3] and only those of AFS I and II (minimal and mild endometriosis) were included in the study.

* Cervical Factor – defined by absent or immotile sperm at the time of postcoital tests or SCMC tests despite adequate mucus and normal semen parameter.

* Ovulatory Disorder – defined as absence of ovulation documented by mid luteal serum progesterone levels despite the maximum dosage of 200 mg/day of the ovulating inducing agent Clomiphene or failure to conceive after 6 ovulatory cycles of Clomiphene citrate.

* Idiopathic – infertility of greater than one year duration, with at least one normal semen analysis, postcoital test, mid luteal serum progesterone, hysteroscopy, laparoscopy and MAR test.

* Male Infertility – was defined as sperm parameters less than the WHO lower limits in at least two samples, taken at least one month apart.

The women were stimulated with either Human Menopausal Gonadotrophin (hMG) alone or in combination with Clomiphene citrate (for those not resistant to Clomiphene). The stimulation

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regime was started in a standardised fashion with Clomiphene citrate from day 2 to day 6 of the cycle and hMG from day 3 to day 7. All patients were monitored for adequacy of ovarian response with transvaginal ultrasound scan on day 8 or 9 of the cycle. Additional doses of hMG were given with a 2-day interval of follicle tracking scans. Measurements in at least two perpendicular diameters of individual ovarian follicles were obtained. When there were 2 to 4 follicles measuring greater than 16mm in maximum diameter, human chorionic gonadotrophin (hCG) 5000 IU was given intramuscularly. Approximately 36 to 40 hours later, Intra-Uterine Insemination (IUI) was performed. A second IUI was performed another 24 hours later. In hMG alone cycles, additional injections of hCG 1000 IU were given on days 4, 7 and 11 after initial hCG injection for luteal phase support.

Semen for IUI was collected by masturbation after approximately 48 hours of abstinence. After liquefaction occurred, the semen was prepared using the swim-up method. If a significant amount of debris was encountered, the semen was prepared using miniPercoll method. The sperm pellet was resuspended in 0.3 – 0.4 ml of media and assessed for sperm density and motility. IUI was accomplished by delivering the sperm concentrate into the uterine cavity with either the K-Jill catheter or a 6.0 Fr suction catheter.

Pregnancy tests were performed 17 days after the first IUI. Pregnancy was defined as the presence of urinary concentration of hCG greater than 50 mIU/mL associated with a delay in menses. Clinical pregnancy was defined as the presence of gestational sac and this was deemed as a viable pregnancy if there was subsequent foetal heart activity.

RESULTS

One hundred and twenty-two couples underwent a total of 245 cycles of superovulation and intrauterine insemination. Thirteen cycles (5.1%) were cancelled mostly because of poor response to the stimulation, recruitment of excessive number of follicles or presence of ovarian cysts. The clinical profile and the distribution of the couples by diagnosis are shown in Table I. When a couple had more than one infertility factor, each factor was tabulated separately.

There were 25 clinical pregnancies, giving a pregnancy rate of 10.8% per completed cycle and 20.5% per patient. Ninety-six percent of these pregnancies occurred in the first or second treatment cycle. There were 3 pairs of twins, one ectopic pregnancy and 6 miscarriages. There were no triplets or quadruplets. The first live birth from this programme were a pair of twins who were delivered by Caesarean section in April 1994. Two patients had moderate Ovarian Hyperstimulation Syndrome and required in-patient monitoring. They subsequently recovered spontaneously.

Table I – Patient characteristics

No. of patients	122
Cycles initiated	245
Cycles cancelled	13
Age (mean ± SD)	31.8 ± 4.4 yr
Duration of infertility	4.1 ± 2.9 yr
Main infertility factors	%
– Endometriosis (AFS I & II)	23.6
– Cervical infertility	7.9
– Ovulatory disorder	46.5
– Male infertility	55.0
– Idiopathic	8.7

Cycle fecundity by cycle attempt and cumulative pregnancy rate

The crude cycle fecundity for all attempts was 0.10 (Table II). No pregnancies were achieved with the fourth or fifth attempts although only a small number of patients made more than three attempts.

The cumulative pregnancy rate was 20% and 96% occurred in the first two attempts. This finding is consistent with that of Remohi et al[4] who reported that 94% of the pregnancies in his series occurred in the first four attempts.

Table II – Overall cycle fecundity & cumulative pregnancy rate by attempt

Cycle No.	Fecundity	
1	15/116	= 0.13
2	9/ 69	= 0.13
3	1/ 34	= 0.03
4	0/ 12	= 0.00
5	0/ 1	= 0.00
Total	25/232	= 0.10

Cycle fecundity by principle diagnostic entity

The pregnancy rate was highest in couples with ovulatory disorders (36% per patient), followed by mild endometriosis (23.1% per patient) and cervical factor infertility (25% per patient). Pregnancies were much poorer in those couples who had male factor infertility (as a large proportion of these had severe semen abnormalities). The cycle fecundity rates and pregnancy rates per patient are shown in Table III.

Table III – Pregnancy rate (PR) by principle diagnosis

Diagnosis fecundity	PR/patient (%)	PR/cycle (%)
Endometriosis (AFS I & II)	3/8 (38)	3/12 (23)
Cervical infertility	2/8 (25)	2/18 (11)
Ovulatory disorder	9/25 (36)	9/57 (16)
Male infertility	10/70 (14)	10/123 (8)
Idiopathic	1/11 (09)	1/19 (5)

Cycle fecundity by female partner's age

The female partner's age was inversely proportional to the cycle fecundity, as shown in Table IV. There were no pregnancies achieved in the group who were over 40 years of age, although they tended to complete at least 4 treatment cycles. This is also in agreement with the findings of Dodson et al[5], who studied 808 cycles of controlled ovarian hyperstimulation and intrauterine insemination.

Table IV – Pregnancy rate (PR) by female's age

Age (year)	PR/cycle (%)
21 – 25	1/ 10 (10)
26 – 30	10/ 62 (16)
31 – 35	11/102 (10)
36 – 40	3/ 52 (05)
> 40	0/ 6 (0)

Cycle fecundity by duration of infertility

The results described as pregnancies per cycle and cycle fecundity are presented in Table V. Those infertile for 1 to 5 years had a

cycle fecundity of 0.13; for 6 to 10 years, of 0.03; and none of the couples who had long standing infertility greater than 10 years conceived. This agrees with the findings of Aafjes et al[6], who reported that the likelihood of treatment-associated pregnancy declined with increasing duration of infertility.

Table V – Pregnancy rate (PR) by duration of infertility

Years of infertility	PR/cycle (%)
≤ 5 yr	24/181 (13)
> 5 ≤ 10 yr	1/ 35 (3)
> 10 yr	0/ 16 (0)

Cycle fecundity by number of motile sperm inseminated

There appeared to be a relationship between the minimum number of motile sperm inseminated and the cycle fecundity. Only one pregnancy occurred when less than one million motile sperm were inseminated. Horvath et al[7] also showed that less than one million motile sperm in the inseminate was essentially ineffective.

DISCUSSION

There are only a few studies that attempt to compare superovulation-IUI with GIFT or IVF. Yovich and Matson[8] obtained a cycle fecundity of 0.09 for supervoluation-IUI patients and 0.30 for GIFT. However, their study was not randomised and did not take into account cancellation rates. Kaplan et al's study[9] showed that although pregnancy rates were higher in GIFT cycles overall, there was no significant difference within some individual diagnostic groups.

Although we did not set out to compare IVF or GIFT with SO-IUI, our results suggest that SO-IUI may have a place for some of our patients before proceeding to these more expensive assisted reproductive technologies. We obtained overall pregnancy rates of 10.8% per cycle and 20.5% per patient. The multiple pregnancy rate was very low, 12% having twins and the incidence of moderate Ovarian Hyperstimulation Syndrome (OHSS) was 0.8%. There were no patients with severe OHSS. When we further analysed our results, we found that the cycle fecundity rate was 0.16, 0.23 and 0.11 respectively for patients with ovulatory disorders, endometriosis and cervical factor infertility. This was even more acceptable when seen in the light of the number of patients who conceived within 3 cycle attempts, that is, 36%, 23% and 25% being the pregnancy rate per patient respectively for these infertility disorders.

Dodson and Havey[5] also considered SO-IUI to be more cost effective than GIFT and IVF when they compared the much higher cancellation rates and higher indirect costs associated with GIFT and IVF. Using the 1988 IVF statistics[10] with mean cancellation rates of 28% for GIFT, they obtained a livebirth rate per cycle of initiated GIFT of 0.15 and for SO-IUI 0.10. For our small series, the cancellation rate was 5% and a livebirth rate per cycle initiated was 0.08. In our centre, the average cost of an SO-IUI was approximately a tenth that of IVF, making SO-IUI a valid therapeutic option for patients.

Further analysis of our study also suggests that while SO-IUI is useful for certain groups of patients, it may be less cost effective to offer it to patients who are over 40 years of age, patients who had severe semen abnormalities or when the total fraction of motile spermatozoa recovered after preparation was less than one million and when the couple had infertility of greater than 10 years duration. In addition, when couples failed to conceive after the second or third cycle of SO-IUI, it may be beneficial to offer them the more sophisticated assisted reproductive techniques.

Lastly, this small study showed that immunological factors were extremely uncommon in our population (less than 1%). We now do not routinely screen all our infertile couples for immunological infertility, thus saving cost for the patient and work for our laboratory.

CONCLUSION

Sophisticated assisted reproductive techniques like IVF-ET and GIFT are expensive, time-consuming, invasive and stressful for infertility patients. For selected groups of patients, a simplified and cheaper alternative such as superovulation with intrauterine insemination can be offered. The rationale for this therapy is the increased gamete density (both oocytes and spermatozoa) at the site of fertilisation. While acknowledging the lack of prospective, controlled studies, this procedure appears to be at least as cost effective as GIFT and IVF in our centre.

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