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Original Article

Treatment of unexplained and mild male factor infertility by In Vitro fertilization and intra-uterine insemination

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Abstract

Objectives: To evaluate the efficacy of in vitro fertilization (IVF) and intra-uterine insemination (IUI) in couples with unexplained and mild male factor infertility. *Methods:* One hundred fifty couples were allocated to treatment with IVF and IUI, both following the same protocol (clomiphene citrate and follicle stimulating hormone (FSH) injection) depending upon their hormonal response. The mild male factor patients were included in the study because we observed that their rate of failed fertilization was not different from those in couples with unexplained infertility. They had ovulatory cycles confirmed by recent ovulatory mid luteal phase progesterone measurement and bilateral tubal patency, which was confirmed by laparoscopy or hysterosalpingography. Men with unexplained infertility had semen analysis with a sperm concentration $\geq 25 \times 10^6$/ml, motility (grdel + 2) $\geq$40% and normal forms $\geq$25%. Men with mild male factor infertility had semen analysis where only one of the above parameters was below the normal range. *Results:* Among the 150 couples, 75 were treated with IVF and 75 were treated with IUI. The mean age of women allocated to IVF was 32.9 years compared to 33.2 years for the IUI treatment group. Cycle day 2 basal plasma estradiol, LH and FSH concentrations were also not different (geometric means; Estradiol 244 and 245 pmol/1, LH 4.9 and 5.3 IU/1, FSH 7.5 and 7.7 IU/1 in the IVF and IUI treatment groups, respectively). *Conclusion:* IUI is the first choice of treatment for unexplained and mild male factor infertility [1] with a lower cost and the equal efficacy as IVF. Treatment delivered within the context of a specialized IVF center will be more efficient and safer because of the potential to salvage over-responding cycles by conversion to IVF.

Key words: unexplained infertility, male factor, IVF, IUI

Introduction

Unexplained Infertility

Unexplained infertility is a diagnosis made by the exclusion, after all the standard investigations have revealed no abnormality. Up to 30% of the couples who are unable to conceive within a sufficient period of time are eventually diagnosed to have unexplained infertility [2]. In a review of unexplained infertility studies, the average cycle fecundity in the untreated control groups was 1.8% in 11 non-randomized studies and 3.8% in 6 randomized studies [3].

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Male infertility

Male infertility is a condition in which the man adversely affects the chances of initiating a pregnancy with his

female partner. The prevalence ranges from 6 to 60%, depending upon the diagnostic criteria. Most commonly these problems arise when man is unable to produce or deliver a fully developed sperm. The incidence of male factor infertility as the main cause of infertility ranges from 30% to 40%.

Causes

Male infertility has many causes, which may be classified into three groups:

a) Pre-testicular - which include the endocrine disorders

b) Testicular - which include deficient sperm production - globozoospermia, teratozoospermia and necrozoospermia, injury to the testicles, undescended testes on one or both sides or childhood German measles infection, are some of the causative factors

c) Post-testicular causes include blockage of the sperm delivery routes, antisperm antibodies and varicose veins around the testicles (varicocele). One key advance in our understanding of male factor infertility is a new and improved interpretation of the sperm concentration and motility values. We know that these semen values do not necessarily predict male infertility. There are men with low sperm concentration but normal sperm fertilizing potential, as well as men with normal concentrations who show diminished fertility [4]. In IVF, with one of the common ovarian stimulation regimes like clomiphene citrate and human menopausal gonadotropin (HMG), which stimulates and sustains the growth of the spontaneously recruited follicles, good results are obtained provided monitoring of endogenous luteinizing hormone (LH) secretion during the late follicular phases is done. Additionally in a review it has been reported that IUI showed improved pregnancy rates compared with ovarian stimulation and timed intercourse [1] and is of value as first line of therapy in patients with unexplained infertility. However, patients who have not conceived after several attempts at IUI may still become pregnant following IVF [5].

Our study is set out to examine patients with unexplained infertility and mild male factor infertility through IVF and IUI treatments and to compare the validity of these treatments.

Materials and Methods

This study was performed on 150 couples between age 30-37 years during a 4 year period from 2003 to 2007. All couples with unexplained or mild male factor infertility that fulfilled the criteria were recruited. These mild male factor patients were included in the study because we observed that their rate of failed fertilization was not different from couples with unexplained infertility. None of the women had previous infertility treatment. They had ovulatory cycles confirmed by recent ovulatory mid-luteal phase progesterone measurement and bilateral tubal patency, which was confirmed by laparoscopy or hysterosalpingography. Men with unexplained infertility had semen analysis with sperm concentration =25x10 ^{6} ml motility (grdel+2) =40% and normal forms =25%. Men with mild male factor infertility had semen analysis where only one of the above parameters was below the normal range. After thorough examination of the reports of 150 couples we explained them the IVF and IUI treatments that they would undergo. We finally categorized 80 patients for IVF and 70 patients for IUI (Table 1)

Table 1. Comparison of semen analysis of patients described as having unexplained infertility and those with mild male factor infertility. Mild male factor was diagnosed when one semen parameter only was below the normal limits for our laboratory, isolated in each variable (concentration, motility and morphology) were detected.

Diagnostic group	Concentration (X10/m) (%)	Motility (%)	Morphology
Unexplained			
Infertility			
IVF (65)	55 (21-132)	50 (44-62)	43 (26-64)
IUI (60)	42 (20-141)	46 (42-55)	39 (25-65)
Mild male factor infertility			
IVF (15)	12 (8-18)	23 (8-34)	43 (26-64)
IUI (10)	11 (7-19)	21 (6-31)	39 (25-65)

IVF – In vitro Fertilization, IUI – Intra uterine Insemination

After full evaluation of the patients and considering exclusion and inclusion criteria D3, recombinant FSH 50IUx2-4 amps. were given, D6 baseline USG to ruleent ovarian cyst was done, and follicular monitoring done

from D9 once 3 follicles of size 18mm x 18 mm was visualized. Injection hCG 10000 was given and IUI/IVF done after 36 hours.

Patients were allocated to the GnRH antagonist cetrorelix dose of 0.25 mg/day, starting from the day in which a follicle ≥13-14 mm in mean diameter was visualized until hCG administration. The control group was monitored in the same way but did not receive GnRH antagonist. In both the groups, 10000 IU hCG was administered when a leading follicle with a mean diameter >18 mm was visualized. In the treatment group, if a leading follicle with a mean diameter >18 mm was detected at the first transvaginal ultrasound scan at the eighth day of the cycle; hCG was administeated the same day without prescribing GnRH antagonist. These cases were included in the treatment group. In both the groups, insemination was performed 30-36 hours after hCG injection.

Inclusion criteria were as follows:

1. Men tested with sperm penetration or migration into cervical mucus
2. Semen analysis showing more than 20 million/ml (WHO Criteria)
3. Men with normal BMI and non-addicts of cigarette smoking, alcohol drinking
4. Detailed clinical, family history and medical history

Exclusion Criteria were as follows:

1. Men with proven genital disorders
2. Men with testicular inflammatory disease (TID)
3. Men with diabetes, hypertension
4. Men more than 35 years of age

Baseline characteristics of couples according to treatment group are as follows:

1. Age (years)
2. BMI (kg/m^2)
3. Previous pregnancies in female partner
4. Deficient sperm production globozoospermia, teratozoospermia and necrozoospermia; injury to the testicles, undescended testes on one or both sides
5. Blockage of the sperm delivery routes, antisperm antibodies and varicose veins around the testicles (varicocele)
6. Endocrine disorders
7. Alcohol and smoking habits
8. Occupation and education

Treatment Protocol

Blood samples were obtained on day 2 of the cycle for the measurement of FSH, LH and estradiol. Ovarian stimulation was started provided both FSH and LH concentrations were <10 IU/1 and estradiol was <200 pmol/l. Clomiphene citrate (50mg daily) was given from day 4 to day 8 of the cycle followed by FSH at a dose of 75 IU daily (IUI) or 150 IU daily (IVF) from day 7 of the cycle. On day 10, patients were monitored with plasma LH and estradiol determination and ultrasound scan to count the number of follicles.

FSH administration and monitoring were continued daily until either the leading follicle reached 17.5mm diameter or spontaneous LH surge was detected. In addition, the IVF group collected a second blood sample in the evening for more accurate detection of possible LH surge and hence timing of egg recovery. The criteria for giving an ovulatory dose of HCG (5000 IU) were ≤3 follicles of >16 mm diameter and estradiol concentration measurement of >1000 pmol/1 per follicle for IUI or ≥3 similar follicles for IVF. If the start of a spontaneous LH surge was detected (previously low LH concentrations rising to >10 IU/1, HCG was still given to 'top-up' the spontaneous LH surge. Intrauterine insemination with prepared semen was planned for 24-48 hours following HCG administration or the spontaneous LH surge, whichever came first. Egg recovery and IVF were more carefully times for 30-35 hrs after HCG administration or the start of the LH surge in the group destined to have IVF. Egg collection was achieved using transvaginal ultrasound (Combison 310; Kretztechnik, AG, Tiffenbach, Austria) as a simple outpatient procedure. No more than three embryos (as required by the human fertilization and embryo transfer authority) were replaced 48-72 hours after egg recovery. Patients in both the groups were given luteal support with dehydrogesterone 10 mg t.d.s. until a pregnancy test was performed 14 days post ovulation.

The data was analyzed to include all pregnancies (live births, clinical abortions, ectopics and biochemical pregnancies). Implantation was considered to have occurred if the plasma HCG concentration rose to about 10 IU/1 and a clinical pregnancy was described following identification of an intrauterine gestational sac with positive fetal heart [6].

IVF treatment group

Eighty patients were initially allocated to IVF treatment, 15 of these patients eventually had their treatment converted to IUI (for poor response) but a further 10 patients from the IUI group responded and so were converted to IVF. Thus, 75 couples ended up in the IVF treatment group. Ultimately four cycles were cancelled due to unclear LH profiles. A total of 71 cycles had between them 125 follicles >16 mm diameter (3.7 follicles/ subject) and so proceeded to egg collection; yielding 320 oocytes (5.6 oocytes/subject) of which 190 eggs were considered mature (3.5 'good' oocytes per subject). One hundred and seventy oocytes fertilized (47% of all eggs, 74% of 'good' eggs) and 89 embryos were replaced in 40 women (1.9 embryos/subject). Unexpected total fertilization failure occurred in five cases (four unexplained and one mild male factor). There were 11 cycles with a positive HCG, which gave a positive HCG per cycle rate of 28.9%, and a positive HCG per cycle with embryo transfer of 37.9%. There were seven singleton births, two clinical abortions and two biochemical pregnancies; the live birth rate per cycle at the start was 14 per 75 (18.4%) and at completion was 9/ 40 (24.1%). The mean dose of FSH required per patient was 900 IU, or 12 ampoules [7,8].

IUI treatment group

Initially 70 patients were allocated to IUI treatment, then 15 patients were added from the IVF group and 10 patients were removed and converted to IVF (due to over response). Thus, the IUI group finally consisted of 75 couples. Only two cycles were cancelled again because of anomalous LH profiles. On the day of HCG there were 92 follicles <16mm diameter (2.3 follicles/ subject). A positive HCG was detected in 12 cycles giving a positive HCG rate per cycle-started rate of 28.6% and per cycle with insemination of 30%. There were eight live births (including one twin and one triplet). There was one clinical abortion, 3 ectopics, but no biochemical pregnancies. The live birth rate per cycle started was 14/75 (19%) and per cycle completed 15/75 (20%). The mean dose of FSH required for a patient was 500 IU, or 6.7 ampoules [9,10].

Result

The mean age of women allocated to IVF group was 32.9 years compared to 33.2 years for the IUI group. Cycle day 2 basal plasma estradiol, LH and FSH concentrations were also not different (geometric means; estradiol 244 and 245 pmol/l, LH 4.9 and 5.3 IU/ 1, FSH 7.5 and 7.7 IU/1 in the IVF and IUI treatment groups, respectively). Among the 150 patients, 75 were treated with IVF and 75 were treated with IUI.

Discussion

A wide variety of assisted reproductive techniques are available for couples with unexplained infertility and mild male factor infertility, such as IUI, GIFT, IVF as described in multi center trial [11]. Benefit arises directly from ovarian stimulation and the resultant increase in the number of follicles, oocytes and available embryos, thereby increasing the probability of implantation. Potential advantages of SIVF over SIUI should be that oocyte retrieval overcomes defective ovulation (luteinized, unruptured follicle syndrome) or by observing fertilization in vitro, there is confidence that clearing embryos are present in the uterus. When there are surplus embryos SIVF may have some advantage in that an element of embryos selection can be introduced. However if as a result of applying more regressive stimulation, overall embryo potential is reduced, then that advantage is lost.

Timing is far less critical for IUI than for IVF and this is one of the major advantages of IUI for the treatment of unexplained infertility. In this context IUI remains the most appropriate treatment for mild male factor infertility [11].

Table 2. Sample calculation of the cost per maternity - of treatment using either in vitro fertilization (IVF) or intrauterine insemination (IUI) in equivalent groups of patent Fallopian tubes.

Treatment Component	IVF (n)	IUI (n)
Metrodin	Rs.40,000	Rs.1,100
Monitoring and scans	Rs.1,800	Rs.200
Sperm preparation	Rs.200	Rs.200
Egg collection and culture	Rs.25,000	Nil
Embryo transfer or IUI	Rs.10,000	Rs. 1,000
Total cost (approximately)	Rs.70,000-80,000	Rs.2,500.

Cost effectiveness

A simple breakdown of the component costs of the two treatments, based on current cost in our clinic is shown in Table 2. The cost per maternity, which is the amount that must be spent to achieve confirmed pregnancy with cardiac activity and viable gestation sac was approximately Rs.70,000-80,000/- for the IVF treatment, compared with Rs.2,500/- for IUI treatment.

Combined treatment for IVF and ICSI for 4-5 people at a time reduces the overall cost per patient.

Conclusion

We conclude that IUI is the treatment of choice for unexplained and mild male factor infertility. It will show the same efficacy as IVF (using clomiphene and FSH) provided the treatment is delivered with the same precision (careful monitoring, detection and management of spontaneous LH surge). Treatment delivered within the context of a specialized IVF center will be more efficient and safer because of the potential to salvage over responding cycles by conversion to IVF. From the cost-benefit viewpoint, IUI, with its lower cost per maternity and therefore greater opportunity for repeat treatments, should be available routinely in all assisted conception units. Indeed, the data presented here make it difficult to support the current and widespread practice of using IVF, particularly involving down-regulation, as a first time of treatment for any patient with unexplained and mild male factor infertility[5].

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