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Original article

Intrauterine insemination versus fallopian tube sperm perfusion in non-tubal infertility

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ABSTRACT

Background: Controlled ovarian hyperstimulation (COH) combined with intrauterine insemination (IUI), using a volume of 0.5 ml of inseminate is commonly offered to couples with non-tubal sub fertility. Another method is Fallopian tube sperm perfusion (FSP) which is based on a pressure injection of 4 ml of sperm suspension while attempting to seal the cervix to prevent semen reflux. This technique ensures the presence of higher sperm density in the fallopian tubes at the time of ovulation than standard IUI. The aim of this study was to compare the efficiency of standard intrauterine insemination (IUI) and Fallopian tube sperm perfusion (FSP) in the treatment of non-tubal infertility.

Methods: 200 consecutive patients with infertility in 404 stimulated cycles were included in the study. Those randomized to standard IUI included 100 patients in 184 cycles [158 clomiphene citrate/human menopausal gonadotrophin cycles and 26 Letrozole/FSH cycles exclusively for polycystic ovarian disease patients] (group A). Patients subjected to FSP included 100 patients in 220 cycles (193 clomiphene citrate/human menopausal gonadotrophin cycles and 27 Letrozole/FSH cycles exclusively for polycystic ovarian disease patients] (group B). Swim up semen preparation technique was used in all cases. Insemination was performed in both groups 34–37 h after hCG administration. Standard IUI was performed using 0.5 ml of inseminate. In FSP 4 ml inseminate was used.

Results: In group A (184 IUI cycles in 100 patients), 22 clinical pregnancies (presence of gestational sac with fetal cardiac activity) occurred (11.95% per cycle over four cycles). In group B, (220 cycles of FSP in 100 patients), 48 clinical pregnancies occurred (21.81% per cycle over four cycles) and this difference was statistically significant ($p < 0.05$).

Conclusions: For non-tubal sub fertility, the results indicate clear benefit for FSP (Fallopian tube sperm perfusion) over IUI (Intrauterine insemination).

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Introduction

Intrauterine insemination (IUI) with mild ovarian stimulation has been used for many years in the treatment of non-tubal infertility. During IUI, pretreated semen is concentrated in a small volume of 0.5 ml and deposited by a catheter into the uterine cavity. The overall pregnancy rates reported in the

literature ranged from 5.7% to 17.7% per cycle.¹ Although the number of available oocytes can be increased by ovarian stimulation, the pregnancy rates in IUI are still not promising, mainly because of suboptimal spermatozoa at the site of fertilization.² An alternative procedure, termed Fallopian tube sperm perfusion (FSP), has been reported with improved pregnancy rates in comparison with IUI.^{3–5} In FSP sperm

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preparation is identical to the used with IUI, but the spermatozoa are diluted in a larger volume of medium up to 4 ml.⁶ This volume has been considered sufficient for bilateral passage of the spermatozoa through the fallopian tubes. Theoretically this would increase the density of capacitated spermatozoa near the oocytes and results in the higher pregnancy rates. A prospective randomized study was designed to determine whether FSP resulted in higher pregnancy rates than IUI.

Material & methods

Two hundred infertile patients, aged 17–39 years, undergoing 404 consecutive cycles of ovarian stimulation were studied from Jun 2007 to Jan 2009. Institutional board approval was obtained. These patients underwent a basic infertility workup, including confirmation of tubal status by hysterosalpingogram or laparoscopy; hormone profile, including serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin and thyroid hormone tests. Menstrual cycle day 3 basal transvaginal ultrasonography was done in all cases to rule out ovarian cysts prior to ovulation stimulation. Exclusion criteria were age >39 years, obstructed fallopian tubes, and cases with marked oligospermia sperm count $<10 \times 10^6$ per ml.

The patients were classified for purpose of etiology of infertility as having mild and moderate endometriosis; ovulatory disorders (hormonal profile and transvaginal sonography characteristic of polycystic ovarian syndrome); cervical hostility (poor properly timed post-coital test); male sub fertility (as per WHO criteria)⁷; unexplained infertility (where no infertility causes were found).

These patients underwent ovulation induction with either clomiphene citrate and Human menopausal gonadotrophin (170 patients) or Letrozole and FSH used exclusively for polycystic ovarian disease patients (70 patients). The ovarian stimulation protocol of clomiphene and hMG (Human menopausal gonadotrophin) was used in 170 patients. It consists of clomiphene citrate 100 mg daily on days 3–7 of the cycle, and 75 IU daily of hMG (Human menopausal gonadotrophin) on days 6–9 of the cycle. For some of the women, hMG was increased to 150 IU in subsequent cycles, depending on the previous ovarian response. Rotterdam ESHRE consensus workshop criteria (2003) used for diagnosis of PCOS. In all PCOS patients (70 patients), who had been on Metformin 500 mg t.i.d, Letrozole was given orally in a dose of 2.5 mg/day for 5 days starting from the third day of a spontaneous or progesterone induced menstrual bleeding. Injection purified FSH 75 IU administered on 6–9 day of menstrual cycle.

Cycles were monitored from day 9 onwards by transvaginal ultrasound measurement of the number and diameter of the growing follicles, the thickness and the morphology of the endometrium. A dose of 10,000 IU human chorionic gonadotrophin (HCG) was administered when at least one leading follicle had reached a diameter of 17–18 mm and at least 8 mm endometrial thickness with tri laminar 'halo' appearance seen. Patients were called 34–36 h later, and either standard IUI (group A: 184 cycles in 100 patients) or FSP (group B: 220 cycles in the 100 patients) was performed. The patients were counseled about the two alternative procedures and

informed consents were obtained before randomization. Patients were allocated randomly to standard IUI or FSP on the day of the insemination in the first cycle itself, according to even or odd serial number in the register. Maximum of four cycle treatments of IUI or FSP was considered for those patients who could not conceive in previous attempts. However those who failed to conceive with IUI were offered IUI only and vice versa.

132 male partners were normozoospermic with count $>20 \times 10^6$ sperm per ml, $>50\%$ motile with forward progression (categories a and b) within 60 min of ejaculation and $>60\%$ morphologically normal spermatozoa (WHO criteria).⁷ Male partners with sperm count ranging from 10×10^6 to 20×10^6 were asked to produce a second semen sample within 2 h of the first sample on the day of insemination. Sixty-eight males having sub fertility as per WHO criteria did consent to the study. However 04 could not produce a second sample at the time of IUI, and 1 patient had total immotility and was excluded from the study. A fresh ejaculate was delivered in a sterile 60 ml jar by masturbation on the day of insemination. Neat semen was left at room temperature for liquefaction for 30 min. The liquefied semen samples were analyzed for density and motility using a fixed-depth counting chamber (Makler). The liquefied ejaculate transferred to a labeled sterile 14 ml round-bottomed disposable centrifuge tube (Falcon No. 2095) and 4 ml flushing media (Medicult) added. After thorough mixing the sample centrifuged at 5000 rpm for 10 min. Then, the supernatants are discarded and the pellet was resuspended and mixed in 3 ml of fresh flushing media (Medicult) and centrifuged for second wash again at 5000 rpm for 10 min. Once again the supernatants were discarded. Each pellet is now gently layered with 0.5 ml for IUI and 4 ml for FSP of universal IVF media (Medicult), and incubated at 37°C in a humidified incubator with 5% Carbon dioxide for 1 h. Post wash semen analysis was done in all cases using Makler's counting chamber before insemination.

Intrauterine insemination was performed with conventional catheter using 0.5 ml of inseminate. To eliminate dead space problem, IUI catheter was first attached to syringe and then inseminate was aspirated. In FSP 4 ml inseminate was used and backflow of inseminate was occluded at the cervical opening by the long size Allis clamp (Fig. 1), which was suitably modified by attaching cervical occluding prongs with rubber cushions to avoid trauma to the cervix and was kept in place for about 3–4 min after insemination. In both groups, the patient rested for 30 min after insemination and received oral micronized progesterone 100 mg, two tablets per day for luteal-phase support.

Values were recorded as mean $\pm$ SD using Microsoft Excel version 4. Statistical analysis was performed using students t-test for testing significance of difference between the means and the χ^2 test to compute p-values for testing the agreement between observation and hypothesis (discrete data). The significance was defined as $p < 0.05$.

Results

The patient characteristics for group A and B were not significantly different concerning patient's age (28.42 ± 2.78

Fig. 1 – Modified allis clamp used for FSP.

years and 28.19 ± 2.80 years), type of sterility (primary infertility 74% versus 72% respectively), and duration of infertility (5.6 ± 2.1 and 5.3 ± 1.9 years respectively). The clinical indications for IUI or FSP were also not significantly different for the two groups (endometriosis 12% versus 12%, polycystic ovarian syndrome 34% versus 36%, cervical 4% versus 4%, unexplained 18% versus 12% and male factor sub fertility 32% versus 36% respectively). The ovarian stimulation protocol for

group A and B were not significantly different (clomiphene citrate/hMG 85% versus 87% and Letrozole/FSH 15% versus 13% respectively). The parameters of cycle monitoring for group A and B including number of follicles ≥ 17 mm diameter (3.93 ± 1.37 versus 3.90 ± 1.17), endometrial thickness on the day of hCG (9.19 ± 0.58 mm versus 9.14 ± 2.1 mm) and the number of spermatozoa ($38.83 \pm 16.57 \times 10^6$ versus $36.68 \pm 13.44 \times 10^6$) inseminated were not significantly different. However the day of hCG (12.8 ± 3.4 versus 11.1 ± 2.1) had been significantly different between the two groups as shown in Tables 1 and 2.

Clinical pregnancy was defined by the presence of fetal cardiac activity, detected by ultrasound examination. Pregnancy rates were similar when compared for the etiology of infertility: for ovarian (PCOS) cause (17.7% versus 21.8%), endometriosis cause (8.4% versus 10.1%), for male infertility (12.8% versus 16.4%) and for unexplained infertility (14.4% versus 24%) for the two groups, respectively as shown in Table 3. There was statistically significant difference ($p < 0.05$) in the overall pregnancy rate per cycle over four treated cycles (11.95% per cycle for IUI versus 21.81% per cycle for FSP over four cycles) as shown in Table 4. Two missed abortion occurred among the patients in group A (IUI) and one twin pregnancy. Three missed abortions occurred among the patients in group B (FSP) as well as two twin pregnancies. However, this limited number of abortions and multiple pregnancies are too low to allow testing for statistical significance. Three cases of mild ovarian hyper stimulation syndrome (OHSS) occurred in both groups.

Discussion

The purpose of this prospective, randomized study was to study pregnancy rates in couples with nontubal infertility when treated with FSP (inseminate volume 4 ml), in comparison with standard IUI (inseminate volume 0.5 ml). Pregnancy rates were 21.81 and 11.95% respectively over four treatment cycles. The same protocols for ovarian stimulation were used in both groups. There was no statistically significant

Table 1 – Type of Infertility, clinical indications and ovarian stimulation protocols in group A (IUI) and B (FSP).

	Group A (standard IUI) (100 patients, 184 cycles)	Group B (FSP) (100 patients, 220 cycles)	t-value	p-value
Type of infertility				
Primary infertility	74%	72%	0.450	0.652
Secondary infertility	26%	28%	0.450	0.652
Clinical indications for IUI/FSP				
Endometriosis	12%	12%	0.000	1.000
Ovulatory dysfunction	34%	36%	0.419	0.675
Cervical factor	4%	4%	0.000	1.000
Male factor	32%	36%	0.844	0.399
Unexplained	18%	12%	1.695	0.090
Ovarian stimulation methods				
Clomiphene citrate/hMG	(85%) (158 cycles in 86 patients)	(87%) (193 cycles in 88 patients)	0.579	0.563
Letrozole/FSH	(15%) (26 cycles in 14 patients)	(13%) (27 cycles in 12 patients)	0.579	0.563

Differences between groups A and B were not statistically significant as $p > 0.05$.

hCG = human chorionic gonadotrophin; IUI = intrauterine insemination, FSP = Fallopian tube sperm perfusion; hMG = human menopausal gonadotrophin, FSH = follicle stimulating hormone.

Table 2 – General characteristics, ovarian stimulation protocols, number of follicles, endometrial thickness on hCG administration and number of motile spermatozoa in groups A (IUI) and B (FSP).

	Group A (standard IUI) (Mean $\pm$ SD) n = 184 cycles	Group B (FSP) (Mean $\pm$ SD) n = 220 cycles	t-value	p-value
Age (years)	28.42 $\pm$ 2.78	28.19 $\pm$ 2.80	0.825	0.409
Duration of Infertility (years)	5.6 $\pm$ 2.1	5.3 $\pm$ 1.9	1.506	0.132
No. of follicles $\geq$ 17 mm diameter	3.93 $\pm$ 1.37	3.90 $\pm$ 1.17	0.237	0.812
Endometrial thickness (mm) On the day of HCG	9.19 $\pm$ 0.58	9.14 $\pm$ 0.50	0.930	0.352
Number of sperm inseminated($\times 10^6$) ^a	38.83 $\pm$ 16.57	36.68 $\pm$ 13.44	1.440	0.152
Day of hCG administration	12.8 $\pm$ 3.4	11.1 $\pm$ 2.1	6.146	0.000

Differences between groups A and B were not statistically significant except day of hCG administration.
hCG = human chorionic gonadotrophin; IUI = intrauterine insemination, FSP = Fallopian tube sperm perfusion; CC = clomiphene citrate;
hMG = human menopausal gonadotrophin, FSH = follicle stimulating hormone.
a Total number of spermatozoa with forward progressive motility.

difference regarding the age of the patients treated, the mean number of follicles, endometrial thickness on the day of hCG administration and the total number of motile spermatozoa inseminated. However the day of hCG (12.8 $\pm$ 3.4 for FSP versus 11.1 $\pm$ 2.1 for IUI) administration was statistically different between two groups (*p* value <0.05).

Kahn et al. reported the first clinical experience with FSP. In their study, they used a Frydman catheter for FSP and reported a pregnancy rate per cycle of 26.9% in patient with unexplained infertility and of 2.7–7.7% in patients with other etiologies. These excellent results, particularly in patients with unexplained infertility, were confirmed by other studies.⁸ Some investigators used a pediatric Foley catheter, a cervical clamp double-nut bivalve speculum and a very encouraging results were reported by Fanchin et al., in which FSP using an auto blocking device (FAST system) doubled their pregnancy rate from 20% to 40%.¹ The different types of catheters used for IUI have been compared but no study reported a significantly higher rate of pregnancy with any one of the catheters tested.^{9,10}

The FSP increases the intrauterine pressure, 70–200 mmHg, necessary for a flush influx of spermatozoa directly into the fallopian tubes. The high pregnancy rate per cycle for FSP as compared with standard IUI could be due to several causes as follows: first, the pressure injection of inseminate can either remove and/or circumvent transitory or partial obstruction of fallopian tubes, such as that created by thick mucus or tubal polyps; second, the concentration of motile spermatozoa around the oocytes after FSP is higher than that obtained after standard IUI; and third, FSP leads to the inseminate

overflowing into the pouch of Douglas. The more accepted hypothesis is the existence of a similar mechanical effect created following a hysterosalpingography.¹⁰

In this study, we tried to evaluate FSP not only in patients with unexplained infertility but also in patients with other causes of infertility including male causes. Two different stimulation regimes were used; however, the distribution of the two types of stimulation protocols (clomiphene citrate/hMG and Letrozole/FSH) appeared homogenous in both studies groups.

Clinical pregnancy was defined by the presence of fetal cardiac activity, detected by ultrasound. When comparing the pregnancy rates in both IUI and FSP in relation to the etiology of infertility, it is found to be statistically similar as shown in Table 3. Though the pregnancy rate of FSP in PCOS and unexplained infertility group of patients is superior to IUI but this finding is statistically not significant. This analysis revealed that couple suffering with any specific etiological sub fertility did not benefit from FSP over IUI.

However, there was statistically significant difference in the overall pregnancy rate per cycle over four cycles of treatment (11.95% per cycle over four cycles for IUI versus 21.81% per cycle for FSP over four cycles) as shown in Table 4 (*p* value <0.009). Pregnancy rates have improved in subsequent attempts with FSP in comparison to IUI. The cumulative pregnancy rates even after the second attempt, over two cycle treatment, were also statistically significant (*p* value <0.03), however there was no statistical difference when each attempt of treatment cycles were compared between the two groups (*p* value >0.05).

Table 3 – Clinical pregnancies (%) per cycle in relation to etiology of the infertility.

	Group A (standard IUI) patients 100 (cycles = 184)	Group B (FSP) Patients 100 (Cycles = 220)	t-value	p-value
Mild/Moderate Endometriosis (CC+hMG protocol)	8.4% (12 patients, 24 cycles)	10.1% (12 patients, 27 cycles)	0.584	0.558
PCOS (Letrozol+FSH protocol)	17.7% (34 patients, 61 cycles)	21.8% (36 patients, 79 cycles)	1.027	0.304
Cervical causes (CC+hMG protocol)	0% (4 patients, 7 cycles)	0% (4 patients, 9 cycles)	0.000	1.000
Unexplained (CC+hMG protocol)	14.4% (18 patients, 33 cycles)	24% (12 patients, 26 cycles)	2.419	0.160
Male subfertility (CC+hMG protocol)	12.8% (32 patients, 59 cycles)	16.4% (36 patients, 79 cycles)	1.016	0.310

IUI = intrauterine insemination, FSP = Fallopian tube sperm perfusion; CC = clomiphene citrate; hMG = human menopausal gonadotrophin, FSH = follicle stimulating hormone; PCOS = Polycystic ovarian syndrome.

Table 4 – Clinical pregnancies (%) per cycles in relation to number of attempted treatment cycles in group A (IUI) and group B (FSP).

IUI Treatment Cycle	FSP						t-value	p-value
	No. of cycles	No. of pregnancies	Pregnancy rate (%)	No. of cycles	No. of pregnancies	Pregnancy rate (%)		
First	100	16	16.00	100	24	24.00	1.414	0.158
Second	40	4	10.00	66	16	24.24	1.816	0.072
Third	30	2	6.66	34	06	17.64	1.326	0.189
Fourth	14	0	0	20	02	10.00	1.374	0.178
Total	184	22	11.95	220	48	21.81	2.599	0.009

IUI = intrauterine insemination, FSP = Fallopian tube sperm perfusion.

Four studies^{2,4,6,11} mentioned a maximum of three cycles per couple; one study¹² reported a maximum of four cycles. We also allowed maximum four cycle treatments of IUI or FSP before considering them for In vitro fertilization and embryo transfer (IVF-ET).

The type of catheter has no impact on the pregnancy rate after intrauterine insemination.¹³ We suitably modified the long size allis clamp, by attaching cervical occluding prongs with rubber cushions, and which was kept in place for about 3–4 min after insemination to prevent any significant reflux. Mild reflux does not seem to influence the results of the FSP but the significant reflux (>0.4 ml) may reduce the pregnancy.^{14,15,17} If more than 1 ml comes back in the catheter, the operator need to wait for a few minutes and re-inseminate again. All of the authors agreed that the women tolerated the FSP technique very well. In our study some patients complained of post insemination pelvic transient pain, more so in FSP than in IUI. Other interesting domain of FSP application is the immunological infertility in the presence of anti-spermatozoa antibodies. The existence of these antibodies does not always correlate with infertility.^{15,16}

In this study by comparing the overall results, we conclude that FSP over four cycles of treatment attempts offers an advantage over the standard IUI, and could replace the IUI in certain indications for artificial insemination. However FSP is more expensive than IUI due to the increased media usages. It could be used as an alternative for couples with non-tubal infertility before embarking on IVF treatment.

Conflicts of interest

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REFERENCES

- Fanchin R, Olivenness F. A new system for fallopian tube sperm perfusion leads to pregnancy rates twice as high as standard intrauterine insemination. *Fertil Steril*. 1995;64(3):505–510.
- Kahn JA, Sunde A, Von During V, et al. Treatment of unexplained infertility. *Acta Obst Et Gyn Scan*. 1993;72(3):193–199.
- Trout SW. Fallopian tube sperm perfusion versus intrauterine insemination: a randomized controlled trial and meta-analysis of the literature. *Fertil Steril*. 1999;71(5):881–885.
- Ng EHY, Makkar G. A randomized comparison of three insemination methods in an artificial insemination program using husbands' semen. *J Reprod Med*. 2003;48(7):542–546.
- Nuojou-Huttunen S, Tuomivaara L, Juntunen K. Comparison of fallopian tube sperm perfusion with intrauterine insemination in the treatment of infertility. *Fertil Steril*. 1997;67(5):939–942.
- Gregoriou O, Pyrrgiotis E, Konidaris S. Fallopian tube sperm perfusion has no advantage over intra-uterine insemination when used in combination with ovarian stimulation for the treatment of unexplained infertility. *Gynecol Obstet Invest*. 1995;39:226–228.
- World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Sperm Cervical Mucus Interaction*. WHO laboratory manual. Cambridge: Cambridge University Press; 1992.
- Mamas L. Comparison of fallopian tube sperm perfusion and intrauterine tuboperitoneal insemination: a prospective randomized study. *Fertil Steril*. 2006;85(3):735–740.
- Smith KL, Grow DR, Wiczky HP, et al. Does catheter type effect pregnancy rate in intrauterine insemination cycles? *J Assist Reprod Genet*. 2002;19(2):49–52.
- Noci I, Dabizzi S, Evangelisti P, et al. Evaluation of clinical efficacy of three different insemination Techniques in couple infertility. *Minerva Ginecol*. 2007;59(1):11–18.
- Ricci G, Nucera G, Pozzob, et al. A simple method for fallopian tube sperm perfusion using a blocking device in the treatment of unexplained infertility. *Fertil Steril*. 2001;7(suppl 1):1242–1248.
- Biacchiardi CP, Revelli A, Gennarelli G, et al. Fallopian tube sperm perfusion versus intrauterine insemination in unexplained infertility: a randomized, prospective, crossover trial. *Fertil Steril*. 2004;81(2):448–451.
- Vermeylen AM, D'Hooghe T, Debrock S, et al. The type of catheter has no impact on the pregnancy rate after intrauterine insemination: a randomized study. *Hum Reprod*. 2006;21(9):2364–2367.
- Kahn JA, von During V, Sunde A, et al. Fallopian tube sperm perfusion. First clinical experience. *Humanit Rep*. 1992;7:19–24.
- El Sadek MM, Amer MK, Abdel-Malak G. Questioning the efficacy of fallopian tube sperm perfusion. *Humanit Rep*. 1998;13(11):3053–3056.
- Elhelw B, Matar H, Soliman EM. A randomized prospective comparison between intrauterine insemination and two methods of fallopian tube sperm perfusion. *Middle East Fertil Soc J*. 2000;5(1):83–84.
- eldeem Hassan Maher Shams. Fallopian tube sperm perfusion in treatment of nontubal subfertility: is it crucial step prior to ART? *ISRN Obstet Gynecol*. 2011:160–167.