Is the fallopian tube better than the uterus? Evidence on intrauterine insemination versus fallopian sperm perfusion

Arne Sunde[1], Jarl A. Kahn[2]

[1]*Fertility Clinic, St. Olav's University Hospital in Trondheim, N-7006 Trondheim Norway.*
[2]*Fertility Clinic, Telemark County Hospital, N-3901, Porsgrunn, Norway.*

Correspondence at: arne.sunde@ntnu.no

Abstract

Fallopian tube sperm perfusion (FSP) is in short comprised of mild ovarian stimulation with the aim of maturing 2 follicles, ovulation induction and insemination using a large volume (4 ml) of inseminate. Perfusion studies demonstrated that with this large volume, the inseminate will fill the uterine cavity, flow through the fallopian tubes and some of it will end up in the peritoneal space. The rational being that this maximizes the chances the gametes will meet and fertilization occur.

We initiated a prospective randomized study that showed that FSP gave higher pregnancy rates compared to conventional intrauterine insemination (IUI), OR: 4.1, (1.2-13.4 95% Confidence interval).

In our hands, FSP seems to give the best results in couples with unexplained infertility.

In the years 1990 to 2002, 1005 inseminations with husband's semen were carried resulting in 141 pregnancies and 112 deliveries. In the same period, 1200 inseminations with frozen donor semen were carried out giving 333 pregnancies and 226 deliveries.

Several studies from other research groups have tried to elucidate whether FSP or IUI will give the highest pregnancy rates in the treatment of non tubal/unexplained infertility. Most of these studies are rather small. A complicating factor is that in these studies, different protocols, different utensils and different catheters for performing FSP have been used. This may well have influenced the outcome of the studies and contributed to the fact that currently there is no consensus on whether FSP or IUI is to be advocated.

Key words: Insemination, IUI, FSP, unexplained infertility, non-tubal infertility.

Introduction

Intrauterine insemination has been used for many years to treat infertile couples. Collecting data from a large number of European clinical in the late 80-ties, suggested that there was a great variation in indications, techniques and results (Sunde *et al.*, 1988). Even today, the indications for performing insemination and the way the procedure should be performed are debated.

Conventionally, intrauterine insemination is performed using a relative small volume of inseminate (~0.5 ml). In the end of the 80-ties we wanted to investigate whether the conventional method for intrauterine insemination could be improved by increasing the volume of the inseminate.

Development of the Fallopian tube perfusion

Our aim was to maximize the likelihood of sperm and egg to meet. We should ensure that sperm cells were present not only in the uterus, but in the fallopian tubes and even in the peritoneal space.

Volumetric study

Six patients admitted to the hospital for sterilization volunteered to take part in a volumetric study while

under anesthesia. The man age of the patients was 36 years and the investigation was carried out at the approximate time of ovulation. An IV-pump operating at 0.5 ml/minute was connected to a Frydman catheter (Frydman embryo replacement catheter CCD Paris). The perfusion volume was estimated by measuring the time from start of perfusion until flow of the perfusate out of the distal end of at least one fallopian tube. The mean perfusion volume was 1, 8 ml, ranging from 0.8-2.5 ml based on this data, we chose an insemination volume of 4 ml.

Semen preparation

A classical swim-up technique was normally used. Briefly, the semen was diluted in culture media, centrifuged at 800 g for 10 min. The pellet was resuspended in culture media and centrifuged again: One ml of culture media was carefully placed above the final pellet and incubated for 30 min at 37°C. Motile spermatozoa were then aspirated form the top of the culture medium. For classical IUI, 10-50 million sperm cells were resuspended un 0.5 ml culture media, for FSP the sperm cells were resuspended in 4 ml media. When frozen semen was used, the semen was thawed at the day of insemination and washed three times by centrifugation (800 g, 10 min) and resuspended in culture media. The final pellet was resuspended in 4 ml of culture media. Except for the very first inseminations, we used commercially available culture media from MediCult Denmark.

Hormonal pretreatment

Ovarian stimulation was in the beginning achieved by administering Clomiphene citrate 50 mg daily from cycle day 4 to 8. Human menopausal gonadotrophin (hMG, Humegon Organon) 75 I.U. daily from cycle day 7 to 9. For some of the women, hMG administration was continued depending on the ovarian response. From 1995 and onwards we used recombinant 75 I.U. FSH (Puregon, Organon) instead of hMG. From cycle day 10, ovarian response was monitored by vaginal ultrasound (number and size of the growing follicles) and daily measurements of serum estradiol. Human chorionic gonadotrophin (hCG) (Pregnyl Organon) 5000 IU was administered when at least one follicle was 17 mm. We aimed at maturing a maximum of two follicles (> 15 mm) and considered a serum concentration of ~ 1000 pmol/l/follicle as optimal. We cancelled cycles where the serum estradiol per follicle was too low (< 500 pmol/l/follicle). Cycles with too many maturing follicles (> 4) or too high serum estradiol (> 5000 pmol/l) were either cancelled or converted to IVF-treatment.

Insemination

Insemination was performed 34-36 hours following administration of hCG. Patients were premedicated by administering 10 mg Diazepam 1 hour before insemination. Insemination was performed with the patient in the lithotomy position. The vagina and the cervix were rinsed with sterile saline. For FSP, a 5 ml plastic syringe was filled with 4 ml of the inseminate. A catheter (Frydman embryo transfer catheter, CCD France) was trough the cervical canal and into the upper part of the uterine cavity. The insemination was performed rather slowly (~1 ml/minute). An Allis clamp was placed on the cervix to prevent reflux. The Allis clamp was kept in place for some minutes after insemination.

Treatment with FSP; Results and Discussion

First experience

A total of 139 couples with different infertility diagnosis were offered in total 239 treatment cycles, Pregnancy rates per cycle or per couple varied considerably between infertility diagnosis and the best result was obtained with couples having unexplained infertility (Kahn *et al.*, 1992a). We did not get very encouraging result in couples where the male has reduced semen quality and in general we do not offer couples where the male have reduced semen quality FSP (Kahn *et al.*, 1992a).

Other research groups have on the other hand demonstrated adequate pregnancy rates even with fairly low semen quality (Strandell *et al.*, 2003).

FSP or IUI?

A prospective randomized multicenter study was initiated in order to evaluate whether FSP gave better pregnancy rates that traditional IUI. Couples with unexplained infertility were included in the study Unexplained infertility was defined as:

Female parameters: Gynaecological examination should not reveal abnormalities and the woman should have regular menstrual periods (24-33 days). Ovulation should be evident by at least two biphasic basal body temperature charts band normal serum progesterone concentrations in the luteal phase. Serum levels of SHBG, testosterone, FSH, LH prolactin and TSH had to be in the normal range. A laparoscopic investigation must show normal fallopian tubes and peritoneal conditions. Post-coital test at the time of ovulation must show normal conditions.

Male parameters: Normal semen quality (> 20 million spermatozoa ml, > 50% motile motility grade 3 (scale 1-4), 50% morphologically normal spermatozoa, no detectable anti-sperm anti-

Table 1. — Fallopian tube sperm perfusion (FSP) or Intrauterine Insemination (IUI)?

Reference	Odds ratio of pregnancy (FSP vs. IUI) OR (95% confidence interval)
Kahn *et al.* 1993a*	4.0 (1,2 – 13,4)
Trout & Kemman (1999)	1.8 (1.2 – 2.9)
Cohrane 2004 (Cantineau *et al.* 2004)	1.9 (1.2 – 2.8)
Cohrane 2009(Cantineau *et al.* 2009)	1.2 (0.8 – 1.7)
Cohrane 2009**	2.0 (1.3 – 3.2)

*First study, not a Meta-analysis.
**excluding studies using a Foley catheter.

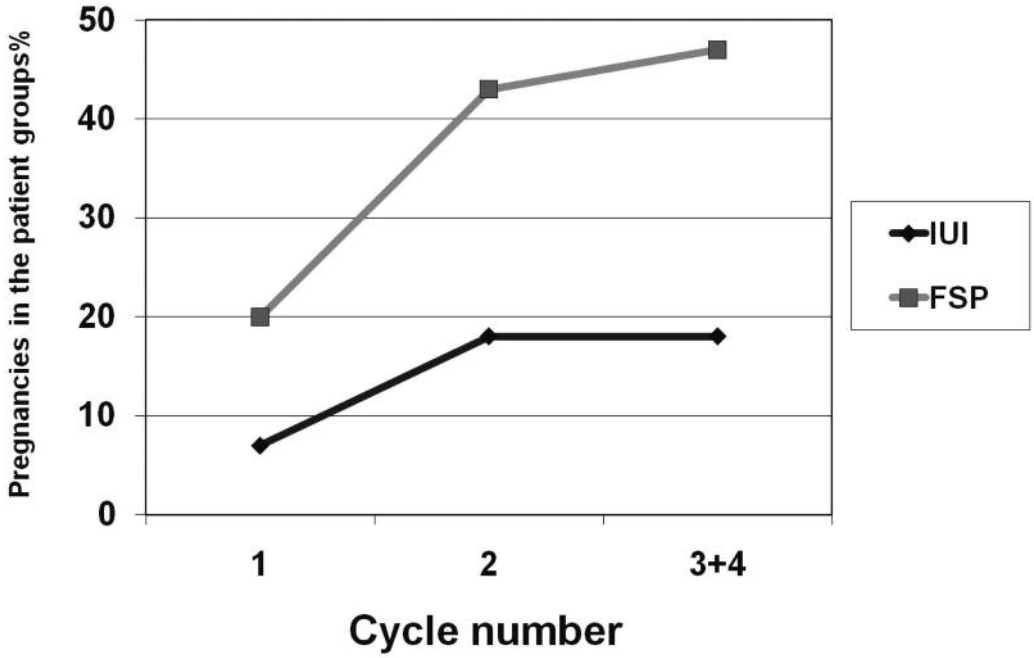

Fig. 1. — Cumulative pregnancy rate in the patient groups randomised either to intrauterine insemination (IUI) or to fallopian tube sperm perfusion (FSP).
Adapted from Kahn *et al.*, 1993a including unpublished data. No pregnancies occurred in the 5th or 6th treatment cycle.

bodies and a normal sperm penetration test. The couples were offered up to 4 treatment cycles.

Outcome in unexplained infertility

We observed a significant higher pregnancy rate both per cycle (26, 9 vs. 9, 8%) and per woman treated (46, 7 vs. 17, 9%) The difference between the groups were statistically significant ($p < 0.05$ χ^2 test, OR 4.0 (1.2 – 13.4) (Table 1 and Fig. 1) (Kahn *et al.*, 1993a).

Several other randomized studies have been done by other clinics with varying results inspiring research groups to do meta-analysis to decide whether the accumulated data were in favor of FSP or not. Trout and Kemman (1999) published in 1999 the first meta-analysis and this was followed in 2004 by a Cohrane analysis (Cantineau *et al.*, 2004). Both these studies concluded that FSP was more efficient that classical IUI (Table 1). The NICE clinical guidelines published in UK in 2004 then advocated the use of FSP in cases of unexplained infertility (NICE guidelines February 2004). Recently a new Cohrane analysis was performed including more studies, suggesting that FSP does not give higher pregnancy rates that classical IUI (Cantineau *et al.*, 2009). One of the new studies included in the recent Cohrane analysis is using a Foley catheter for performing FSP and obtained much better results with IUI than FSP (Biacchiardi *et al.*, 2004). It is a concern that Foley catheters seem to be associated with lower pregnancy rates in FSP (Cantineau *et al.*, 2004, 2009) Computing the Odds ratio of pregnancies omitting the studies using the Foley catheter give an OR of 2,0 (1.3 – 3.2, 95% confidence interval) in favor of FSP (Table 1).

FSP was our standard protocol for the treatment on unexplained infertility from 1990 to 2002. As a

Table 2. — Results obtained with FSP with fresh husbands semen (all indications) in the period 1990 to 2002.

	Numbers	Percentages
Number of started cycles	1340	
Number of cancellations	221*	16.4% of started cycles
Number of insemination	1005	
Number of pregnancies'	142	14.1% of inseminations
Number of deliveries	112	11.1% of inseminations
Number of multiple deliveries	6**	5.4% of births

*95 of these cycles converted to IVF-cycles.
**5 sets of twin one set of triplets.

routine, the patients were offered up to 3 cycles with FSP prior to entering the IVF-program. In this period 1340 cycles were started and 1005 inseminations done resulting in 112 deliveries (Table 2). In 2002, the reimbursement system changed allowing partial reimbursement of drug cost for up to three treatment cycles regardless of type of treatment. This change in the reimbursement system meant that patients rather would spend their "allotted three cycles" on IVF rather than on FSP.

Donor insemination

We tested whether FSP also could give good clinical results using frozen/thawed donor semen. In the first two treatment cycles, we observed a pregnancy rate of 34% and 25% respectively. The outcome was judged to be so favourable that FSP became the standard insemination protocol using donor semen. (Kahn *et al.*, 1992b). In the years 1990 to 2002, we performed in total 1200 donor inseminations using frozen semen with an average pregnancy rate per insemination of 27.8% (Table 3). ICSI was not allowed in Norway until 1996 and ICSI in combination with testicular or epididymal sperm was not allowed until 2004. The use of donor sperm in combination with IVF or ICSI was not allowed until 2004. Semen donors were anonymous in Norway until 2005 when a new law was passed banning anonymous donor insemination. At that time we stopped offering donor insemination.

Number of treatment cycles

We observed a clear relationship between the treatment cycle number and pregnancy rates (Fig. 2). A clear drop in pregnancy rates were observed after the first two treatment cycles and the pregnancy rates in cycles 4 and more were very low. We therefore routinely did not offer more that 3 FSP cycles in cases of unexplained infertility and rarely more that 4 cycles in cases where donor semen is used (Kahn *et al.*, 1992b, 1993b).

Variants of FSP

Since the seminal papers of Kahn *et al.* where published, several variants of FSP has been developed using different form of catheters, clamps and devices to perform the insemination itself including "The FAST System©" (Fanchin *et al.*, 1995), "The DNB speculum" (Mamas *et al.*, 1995) and a different device for blocking reflux (Ricci *et al.*, 2001).

Despite the fact that several randomized studies and ensuing meta-analysis presented data suggesting that FSP is more efficient than standard IUI, the method has not replaced the standard IUI-protocol. FSP is not more complicated to perform than IUI, it is well tolerated by the patients and there are not more side-effects or complications that IUI. A complicating factor in the evaluation of FSP is the fact that several and perhaps less efficient variants FSP have been developed by other research groups

Table 3. — Results obtained with FSP with frozen/thawed donor semen in the period 1990 to 2002.

	Numbers	Percentages
Number of started cycles	1316	
Number of cancellations	116	8.8% of started cycles
Number of insemination	1200	
Number of pregnancies'	333	27.8% of inseminations
Number of deliveries	226	18.8% of inseminations
Number of twin deliveries	36	15.9% of births

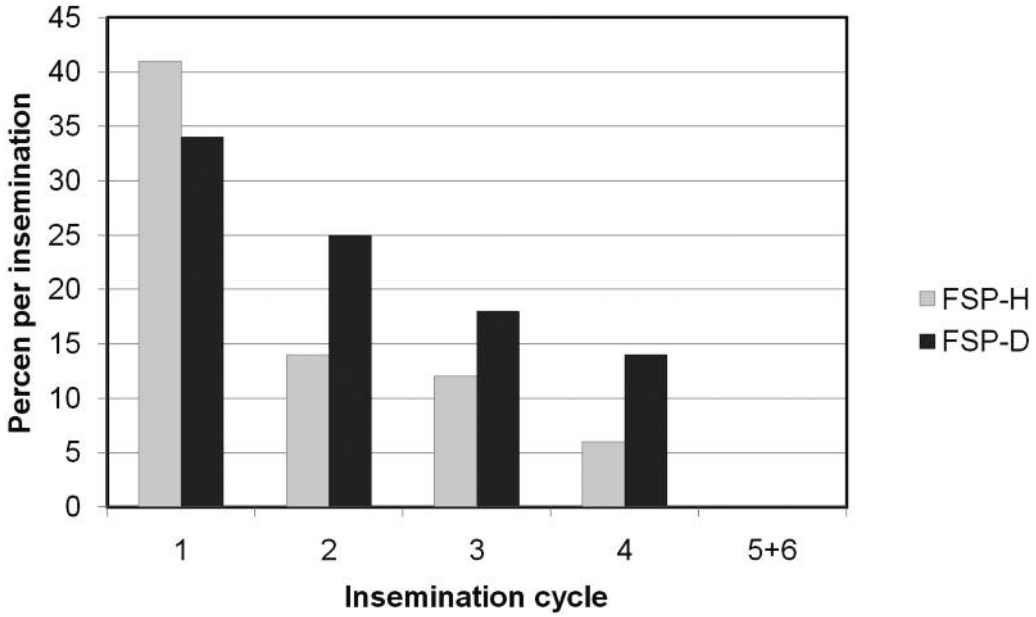

Fig. 2. — Pregnancy rate per insemination versus treatment cycle number, in inseminations with husband's semen (FSP-H) or with frozen donor semen (FSP-H).
Adapted from Kahn *et al.*, 1992b and 1993 b.

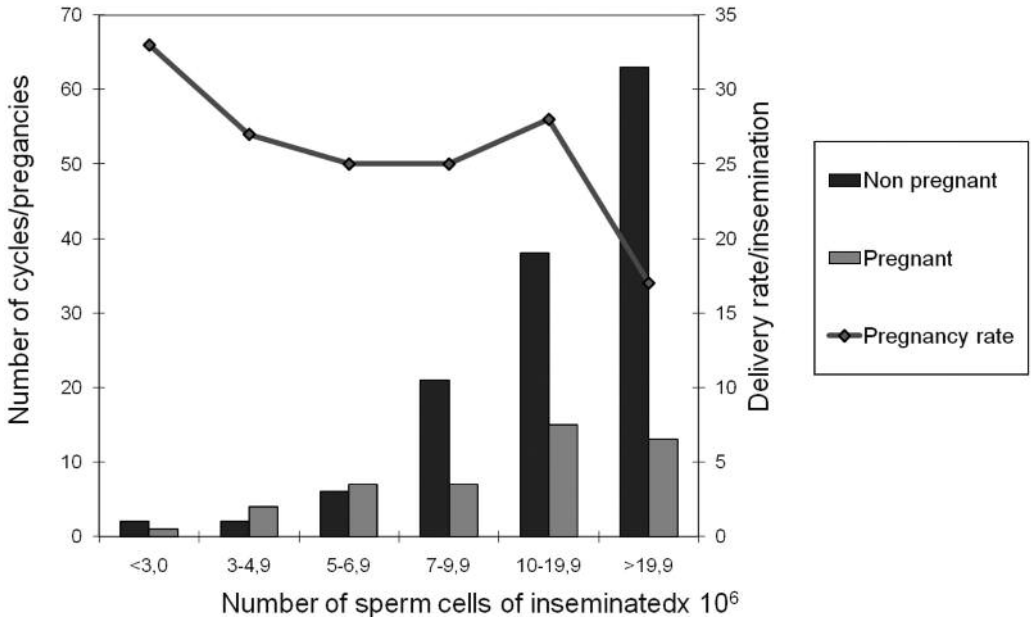

Fig. 3. — Fallopian tube sperm perfusion and male factor. Number of inseminations and number of pregnancies according to the total number of spermatozoa in the inseminate.
Adapted from Strandell *et al.*, 2003.

(Cantineau *et al.*, 2009). One puzzling finding is that two studies using the Foley catheter both reports that IUI clearly gives better results that FSP (Biacchiardi *et al.*, 2004; Nuojua-Huttunen, 1997). This is in contrast to most other published studies where pregnancy rates obtained with FSP was at least as good as, if not better, that the pregnancy rates obtained with IUI. Whether this observation warrants a clear advice not to use the Foley catheter for FSP is still unclear (Cantineau *et al.*, 2004, 2009).

Summary

Several published studies have tried to elucidate whether FSP or IUI is gives highest pregnancy rates in the treatment of non tubal/unexplained infertility. Most of these studies are rather small. A complicating factor is that, in these studies, different protocols, different utensils and different catheters for performing FSP have been used. This may well have influenced the outcome of the studies and

contributed to the fact that currently there is no consensus on whether FSP or IUI is to be advocated. A meta-analysis excluding studies using the Foley catheter for insemination gives however a significant higher pregnancy rate using FSP compared to standard IUI.

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