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Research Article

Should Intrauterine Inseminations be Performed under Ultrasound Guidance?

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Abstract

Objective: To evaluate the impact of ultrasound guidance on ease of cervical catheterization, pregnancy and live birth rate in intrauterine inseminations (IIU) cycles.

Methods: This prospective, monocentric, randomized study was conducted between February 2011 and November 2012 in the ART Unit of the University Hospital of Nantes. Eligible patients undergoing IUI cycles were randomized for ultrasound guidance during IUI. Ease of cervical catheterization, pregnancy and live birth rates were then compared between ultrasound and control (no ultrasound guidance) groups.

Results: A total of 190 cycles performed in 142 patients were analyzed. Among them, 92 IUI cycles were performed under ultrasound guidance, whereas 98 were performed without ultrasound guidance (control group). The proportion of IUI cycles with easy catheterization was similar in the two groups. Finally, the pregnancy rate and the live birth rate were not statistically different between ultrasound and control group.

Conclusion: Ultrasound guidance neither facilitates cervical catheterization nor significantly increases pregnancy and live birth rates in IUI cycles.

Keywords: Intrauterine insemination; Ultrasound; Pregnancy rates; ART; Cervical catheterization

Introduction

Since the early work of Strickler et al in 1985 [1], many studies have focused on the interest of ultrasound guidance for intrauterine embryo transfer in in vitro fertilization (IVF) cycles. Although the most significant studies available to date are in favor of suprapubic ultrasound during embryo transfer [2,3,4,5], this remains controversial in the literature and some authors did not report the same trend towards better clinical outcome when embryo transfer was performed under ultrasound guidance [6,7,8,9,10].

The main argument put forward by authors advocating ultrasound guidance for embryo transfer in IVF cycles is that it facilitates the procedure of cervical catheterization and intrauterine embryo transfer, therefore making it less traumatic [7,11]. Indeed, the proportion of catheters presenting blood after embryo transfer has been reported to be lower under ultrasound guidance [12]. This could be explained by a decreased frequency of endometrial trauma due to a better visualization of the cervico-uterine angle [13] and of the uterine fundus [14]. These two precautions could also result in a reduced frequency of uterine contractions [15,16], that have been described to potentially lead to the expulsion of some of the content placed in the uterus [17,18].

Concerning intrauterine inseminations, it has been shown that the most significant predictive factors of pregnancy were the number of mature follicles on ovulation triggering [19], the duration of infertility [20], female age [21] and the number of motile sperm inseminated [22], this last parameter being potentially negatively influenced in case of uterine contractions caused by traumatic insemination, subsequently potentially affecting pregnancy rate. In parallel to what was done for embryo transfer in IVF cycles, the question of the interest of transabdominal ultrasound guidance in intrauterine inseminations should be raised. To date, only three studies have investigated the value of ultrasound in intrauterine insemination, with many methodological limitations [23,24,25].

The main objective of our study was to assess the impact of suprapubic ultrasonography during IUI on pregnancy and live birth rates. The secondary objective was to assess whether ultrasound guidance could make the act of insemination easier.

Methods

This prospective, randomized study was conducted in the ART unit of the University Hospital of Nantes between February 2011 and November 2012. Randomization between ultrasound guidance and control (no ultrasound guidance) groups was made by lottery, in the absence of the couple. Patients with empty bladder were excluded from the study. There were no other exclusion criteria. The inclusion criteria were female age 20-42 years old, permeable tubes, normal uterus, normal thyroid function, normal prolactin and no history of cervical surgery. Patients not having a full bladder for insemination were systematically excluded, as this could obviously influence the ease of catheterization. For each patient, age, serum Anti-müllerian Hormone (AMH), Antral Follicle Count (AFC), Body Mass Index (BMI) and smoking status were recorded. The eventual diagnosis of polycystic ovary syndrome (PCOS) was based on the Rotterdam

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Table 1: Basal, demographic and stimulation characteristics of patients in ultrasound and non-ultrasound groups. Results are presented as mean (standard deviation) or proportion.

	Ultrasound group	Control group (IUI without ultrasound)	Significance
Number of cycles	92	98	
Age (years)	32.4 (5.5)	32 (5.1)	NS
BMI (kg/m²)	22.1 (4.0)	22.8 (4.3)	NS
Active smoker (%)	19	15	NS
PCOS (%)	27	26	NS
AMH (µg/L)	4.58 (4.6)	5.03 (4.7)	NS
AFC	20.42 (14.5)	23.42 (16.5)	NS
Infertility duration (years)	2.8 (2)	3.1 (2)	NS
Cycle rank 1 (n)	43	39	NS
Cycle rank 2 (n)	34	39	NS
Cycle rank 3 (n)	12	17	NS
Cycle rank 4 (n)	3	2	NS
Cycle rank 5 (n)	0	0	NS
Cycle rank 6 (n)	0	1	NS
Average cycle rank	1.72 (0.8)	1.85 (0.9)	NS
Total FSH used (units FSH)	851.1 (776)	824.1 (685)	NS
Number of follicles ≥ 17 mm	1.206	1.275	NS
Concentration of mobile sperm in the inséminat (millions perml)	5.40 (4.2)	4.90 (3.3)	NS
Oestradiol Day hCG -2 (pg / ml)	249.6 (163)	262.4 (196)	NS
Oestradiol Day hCG (pg/ml)	405.0 (268)	468.2 (299)	NS
Endometrial thickness Day hCG -2 (mm)	6.7 (1.2)	7.0 (1.6)	NS
Endometrial thickness Day hCG (mm)	8.2 (1.9)	7.5 (1.5)	NS

NS: Not significant (p> 0.05)

criteria [26]. Cycle characteristics were also recorded, i.e. amount of exogenous FSH injected, cycle rank, number of follicles >17 mm on the day of hCG, peak estradiol and endometrial thickness. We then calculated the proportion of IUI cycles with easy catheterization and the success rate, i.e. clinical pregnancy rate and live birth rate.

Controlled Ovarian Stimulation (COS) was based on recombinant FSH (Gonal F®, Serono, France or Puregon®, MSD, France) or menotropin (Menopur®, Ferring, France). FSH starting dose ranged from 25 to 300 IU per day, according to ovarian reserve and previous cycles. Monitoring of ovarian response to stimulation was based on transvaginal ultrasound (Siemens Acuson® X150 / EV 9-4) and simultaneous measurement of serum estradiol, LH and progesterone. Monofollicular ovarian response was aimed for in most cases. However, bi or trifollicular ovarian response could sometimes be accepted, according to the prognosis and history of each patient. Ovulation was triggered by recombinant hCG injection (Ovitrelle ®, Serono, France) when at least one follicle reached 17 mm with a serum estradiol >150 pg/ml. The insemination was performed 36 h after ovulation triggering, except in cases of spontaneous LH surge where IUI was performed 12h after hCG injection. In order to avoid IUI on Sundays, a GnRH antagonist (cetrorelix , Cetrotide®, Serono, France) could be administered on Friday evening allowing ovulation triggering to be performed on Saturday and IUI on Monday.

Semen collection was performed in the andrology laboratory after 2 to 5 days of sexual abstinence. Sperm analysis was performed in order to confirm that sample's characteristics were in agreement with IUI. Sperm preparation was based on discontinuous silica gradient (Suprasperm®, Origio®, Lyon, France). After 15 minutes centrifugation at 1500 rpm, the supernatant was discarded and the pellet was washed in 3 ml of culture medium (Universal IVF Medium ®, Origio®) and then centrifuged for 5 minutes at 2000 rpm. The pellet was finally re suspended in 500 to 700 µl of culture medium (Universal IVF Medium®, Origio®). In case of large pellets, a swim up step could be added after density-gradient. Sperm preparation was incubated for at least 1 hour at 37°C under 5% CO2 in order to allow capacitation. Sperm preparation characteristics were checked just before IUI.

All IUI were performed by junior obstetricians and/or gynecologists of the ART unit. Each of them had received one-month training in IUI with or without ultrasound before participating in this study.

In both groups, a flexible soft catheter (Intrauterine standard probe, CCD® laboratory, France) was always used in first-line. In case of any slight difficulty of catheterization, IUI was rated as "difficult." If the catheterization was done gently without any resistance, IUI was rated as "easy". When cervical catheterization was not possible with these soft catheters, the operator changed catheter for a more rigid one (Intrauterine probe shape memory, CCD® laboratory, France), but without using ultrasound if the patient was not part of the ultrasound group. In the ultrasound group, catheterization was performed ultrasound guidance and sperm were placed in the uterus

Table 2: Catheterization characteristics and success rates of IUI cycles in ultrasound and control groups.

	Ultrasound group (n=92 cycles)	Control group (n=98 cycles)	Significance
Number / proportion of pregnancy per cycle	20 / 21,7%	14 / 14,2%	NS
Number / proportion of live birth per cycle	15/ 16,3%	11 / 11,2%	NS
Number / proportion of miscarriages per cycle	5 / 5,1%	3 / 3,06%	NS
Number / proportion of IUI with easy catheterization	73 / 79%	77 / 78,5%	NS
Number / proportion of IUI cycles requesting a change of catheter	5 / 5,4%	9 / 9,18 %	NS

NS: Not significant (p> 0.05)

Table 3: Catheterization characteristics and success rates of IUI cycles in ultrasound and control subgroups when only first rank cycles are considered.

	Ultrasound subgroup (n=43 first rank cycles)	Control subgroup (n=39 first rank cycles)	Significance
Number / proportion of pregnancy per cycle	11 / 20,75%	4 / 10,25%	NS
Number / proportion of live birth per cycle	7/ 16,27%	2 / 5,12%	NS
Number / proportion of miscarriages per cycle	4/9,3 %	2 / 5,12%	NS
Number / proportion of IUI with easy catheterization	34 / 79%	31/ 79,48%	NS
Number / proportion of IUI cycles requesting a change of catheter	3 /6,97 %	5/ 12,82%	NS

NS: Not significant (p> 0.05)

when the catheter was visible in the uterine cavity, while remaining away from the uterine fundus.

In the control group (without ultrasound guidance), IUI was performed according to the usual procedure, sperm preparation being placed in the uterus following the catheter's scale, once the passage of the catheter through the internal orifice of cervix was perceived. All patients were told to remain lying for 5 to 10 minutes after IUI. Luteal phase support was carried out with intravaginal progesterone 200 mg / day (Utrogestan®, Besins, France) until pregnancy test, 14 days after IUI. The patient wise defined as pregnant as soon as the pregnancy test was positive.

Statistical analysis was performed with Medcalc® software (v11.1.1.0). Student's t test was used for comparison of means, and Chi Square test for comparison of proportions. A p value < 0.05 was considered statistically significant.

Results

A total of 209 IUI cycles were eligible for the study, but 19 were excluded because of empty bladder. We finally included 190 IUI cycles performed in 142 patients. A total of 92 cycles were performed with suprapubic ultrasound and 98 IUI cycles were performed without ultrasound (control group). All patients considered in this study had full bladder at the time of IUI. Basal, demographic and stimulation characteristics in both groups are presented in Table 1. Both groups were comparable for all the variables. Each couple underwent 1 to 3 IUI cycles during the study period. IUI cycles outcome are presented in Table 2. No statistical difference was found between ultrasound and no ultrasound groups regarding pregnancy rate, live birth rate, miscarriage rate, and ease of catheterization. In order to account for IUI cycle rank, we did the same analysis in ultrasound and control subgroups only including first IUI cycles. Ultrasound and control subgroups remained comparable in terms of basal and demographic characteristics (data not shown) and the clinical outcome was not significantly different between both groups (Table 3). When IUI cycles with easy catheterization (n=150) were compared to those with difficult catheterization (n=40), the pregnancy, live birth and miscarriage rates were 17.3%, 12.6% and 4.6% versus 20%, 17% and 0% in easy and difficult catheterization groups respectively (p>0.05).

Discussion

In this prospective, randomized study, we report that ultrasound guidance does not have a significant positive impact on clinical outcome and on ease of catheterization in IUI cycles. The randomization allowed us to objectively compare 2 homogeneous groups according to female age [21], body mass index [27], smoking status [28], ovarian reserve [29], number of motile sperm inseminated [30], number of mature ovarian follicles recruited [31] and cycle rank [20], which have been demonstrated to impact pregnancy rates in IUI cycles. We also checked that all patients had full bladder at the time of IUI, as this could influence the ease of catheterization by modifying uterus position, and subsequently impact pregnancy rates [32,33].

Although many studies have been performed on the interest of transabdominal ultrasound guidance in embryo transfer [2,3,4,5], few studies have evaluated its interest in IUI cycles. Our results are in agreement with the study of Ramon et al. [23], who did not find any evidence of increased pregnancy rates when IUI was performed under ultrasound guidance. Comparably to our study, these authors had also taken care to systematically perform IUI with full bladder for both groups. In this study, 106 cycles were performed with ultrasound guidance and 125 without. However, some other authors did not report the same conclusions. Oztekin et al. [24] recently reported their results demonstrating easier cervical catheterization and improved pregnancy rates in IUI cycle when guided by ultrasound. However, it should be noted that the patients who did not benefit from ultrasound guidance systematically had empty bladder. Therefore, this study compared a group undergoing IUI with ultrasound guidance and full bladder to a group not covered by any of these characteristics, thus preventing from yielding final conclusions on the interest of ultrasound guidance alone. As bladder fullness facilitates catheterization, this could account for the improvement in pregnancy rates in this study. This is supported by another study showing improved pregnancy rates in IUI cycles with bladder

fullness alone, which corrects the cervical angle and thus facilitates catheterization and lowers cervix and endometrium trauma [32]. Even more recently, another study reported better pregnancy rates in IUI cycles under ultrasound guidance [25]. In this study, all patients had a full bladder. However, the majority of IUI (64%) were performed by an experienced senior, whereas only 36% were performed by a junior, thus potentially leading to a bias in the interpretation. In addition, the authors stated that the use of ultrasound did not improve pregnancy rates when IUI was performed by a senior. Therefore, the clinician's experience seemed to have a major role, rather than ultrasound guidance itself. One could argue that having full bladder is more beneficial than using ultrasound guidance. However, no high quality study comparing IUI with empty of full bladder has been reported in the literature as far as we know. Whether ultrasound guidance is more important than having full bladder is a question of interest, although it was not the purpose of our study. Further studies could be specifically designed in order to address this issue.

The way ultrasound was performed could also be questioned. Indeed, although transvaginal ultrasound generally offers improved visualization of ovaries than transabdominal ultrasound, this is definitely not the preferred method for IUI, as the presence of the ultrasound probe in the vagina makes the introduction of the catheter in the cervix difficult. Therefore, the benefit-risk ratio of transvaginal ultrasound guided intrauterine insemination would be most probably unfavorable.

Anatomical position of uterus might eventually be considered as an important factor for the success of IUI, even if we could not find evidence in the literature on this particular aspect. Unfortunately, our database was not sufficiently filled out to give reliable information on patients with either antevert or retrovert uterus. Therefore, we could not provide data on the importance of this anatomical point on the success rate and ease of the application. However, the proportion of women with antevert uterus is much higher than with retrovert uterus in our experience. As full bladder helps correcting the cervical angle in these women with antevert uterus, we postulate that the exclusive inclusion of women with full bladder in a population with a large majority of women with antevert uterus nearly rules out the bias of anatomical position of uterus.

Our conclusions could be balanced by the fact that we have not calculated the number of cycle needed to be sure that the differences were not significant before starting the study. In addition, several operators performed the inseminations, which may cause some variability in their achievement even if they were all driven.

In conclusion, this prospective randomized study did not allow us to demonstrate that ultrasound guidance in IUI cycles leaded to easier catheterization and improved pregnancy rates. As all IUI were performed in women with full bladder by trained operators, we hypothesize that ultrasound guidance could eventually be useful for young trainees. According to our results, ultrasound guidance should not be recommended in all IUI cycles, provided that women have a full bladder and that IUI is performed by experienced gynecologist.

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