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Ultrasound-guided intrauterine insemination versus blind intrauterine insemination: a randomized controlled trial

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Summary

Purpose: This study was performed to determine the effects of ultrasound (US) guidance during intrauterine insemination (IUI) on pregnancy rate. *Materials and Methods.* This study is a prospective randomized controlled trial which was performed in Women's Health Research and Education Hospital, Infertility Unit. The study enrolled 130 couples who were scheduled to undergo IUI. The couples were randomized according to a computer-generated list into two groups; 1) the ultrasound-guided IUI group included 64 couples (n = 64) treated for 99 cycles 2) blind IUI group included 66 couples (n = 66) treated for 104 cycles. All women underwent controlled ovarian stimulation before IUI. The study's main measurements were pregnancy rate per cycle; pregnancy rate per woman. *Results*: The pregnancy rates were similar in both the ultrasound-guided (USG)(16.2%, 16/99) and non-ultrasound-guided (NUSG)(12.5%, 13/104) groups (p = 0.386). *Conclusions*: The present results suggest a routine ultrasound guidance during IUI is not essential as it does not increase pregnancy rates but it can be used in such cases to overwhelm some sort of difficulties.

Key words: Intrauterine insemination; Ultrasound guidance; Pregnancy rate.

Introduction

Intrauterine insemination (IUI) is a simple first-base treatment for infertile couples [1]. In comparison with other assisted reproductive techniques (ART), this treatment has been widely used to treat infertile couples with a variety of indications. Common indications include cervical factors, mild endometriosis, mild to moderate male factors, ovulatory dysfunction, and unexplained infertility [2]. The reported pregnancy rate per cycle ranges from 8% to 22% [3-5]. The reported pregnancy rates per IUI cycle are variable due to differences in cause and duration of infertility, ovarian stimulation and methodology, sperm preparation techniques, treatment cycles, and number of times that IUI is performed during a cycle (once or twice) [3-5]. Engels *et al.* reported that pregnancy development is not associated with endometrial volume, but women who developed pregnancy have a significantly higher subendometrial flow index (FI) [6].

In cycles of *in vitro* fertilization (IVF), the embryo transfer process is generally done under abdominal ultrasound (US) guidance. Ultrasound visualization of the endometrial cavity prevents the catheter from touching the uterine fundus. US also allows us to visualize the cervico-uterine angle, reducing the number of difficult cervical catheterizations, as well as cervical manipulation [7]. Many studies have indicated that US guidance during embryo transfer increases the rates of implantation and pregnancy [7,8].

However, only two studies evaluated the use of US during IUI. The catheter striking the uterine wall or cervical manipulation with tenaculum placement increases uterine contraction [9] due to the release of oxytocin or prostaglandin and expulsion of > 40% of the volume introduced into the uterine cavity has been reported [10]. Balci *et al*. reported that uterine contractions during IUI were significantly more frequent with tenaculum usage [11]. However, while uterine contractions increase with tenaculum, pregnancy rates do not decrease; even they may increase [11, 12]. Considering the role of seminal prostaglandins in natural fertilization, vaginal application of misoprostol before the IUI, in order to increase the ratio of conception, did not result with an increase in the ratio of pregnancy [13].

This study was performed to investigate whether the US guidance during IUI improves pregnancy rates. Extra attention was performed to not to touch the fundus during the IUI procedure [14]. The authors utilized US in order to perform IUI by observing that catheter does not get in touch with the uterine fundus and compare the pregnancy results with IUI without US.

Materials and Methods

The study protocol was approved by the Dr. Sadi Konuk Education and Research Hospital Ethical Committee on February 7, 2011 (approval number 2011/2-05). This was a randomized, single-blind, controlled trial comparing the efficacy of US guided (USG) IUI with non-ultrasound guided (NUSG) IUI on pregnancy rate.

The participants were recruited from 173 consecutive couples undergoing infertility counseling at the present ART Unit from February 2011 to July 2011. Figure 1 shows a flowchart of the

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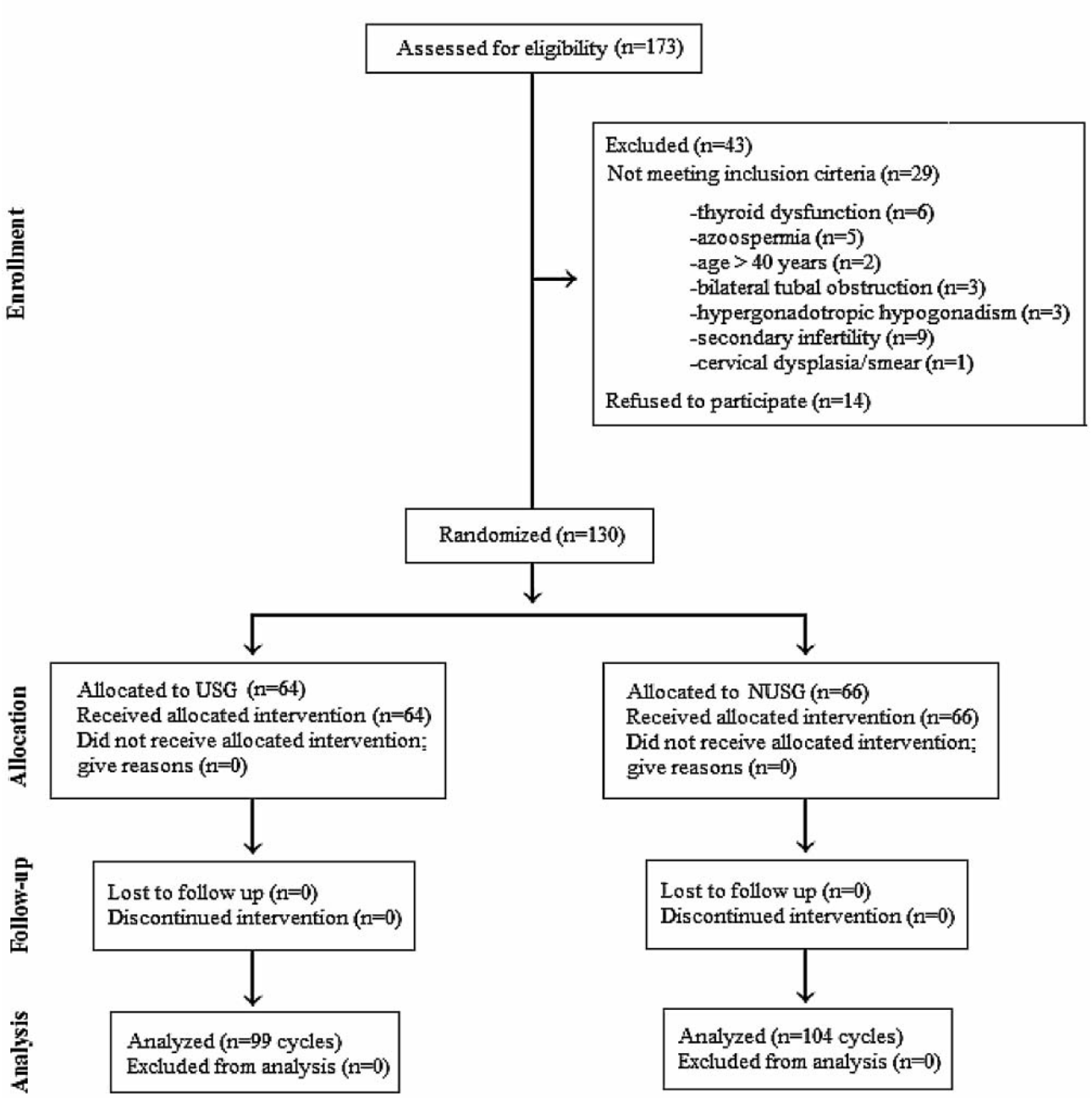

Figure 1. — Flowchart of the study.

study. A total of 130 eligible infertile couples – with mild male factor, idiopathic or anovulatory infertility- were enrolled for the study. All patients were counseled about the nature of the study and gave their informed consent. They were then randomized according to a computer-generated listed in sealed, opaque envelopes into two groups; the USG IUI and NUSG IUI groups.

All the women underwent a standard gynecological examination and cervical screening by the Papanicolau test. The following infertility work-up was performed on all women; hysterosalpingography, transvaginal ultrasonography, basal hormonal assays (on the third day of the spontaneous cycle) and determination of the number of antral follicles. Semen analysis was performed on the samples from all male partners.

Ultrasonic scans were performed via a 200 ultrasound unit equipped with a five to seven MHz endovaginal probe. The numbers of follicles in both ovaries were added up to the total antral follicle count. The follicles visualized and counted by transvaginal sonography in the early follicular phase (on day 3 of spontaneous cycle) were two to ten mm in size. All women had the following basal hormonal assays: estradiol (E_2) follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and prolactin. Serum levels of progesterone were measured on day 21-24 by the chemiluminescence method.

Hysterosalpingography was performed to investigate the shape of the uterine cavity and the shape and patency of the fallopian tubes. Semen analysis was performed by employing visual estimation by microscope.

The exclusion criteria were: older than 40 years, not having a normal uterine cavity and/or bilaterally obstructed fallopian tubes, to be diagnosed as *hypogonadotropic* hypogonadism or *hypergonadotropic* hypogonadism or any dysfunction of thyroid gland or any other coexisting chronic disease, basal FSH level higher than 12 IU/L; male partner's sperm count of less than five million on a washed sample, and being unable to provide fully informed written consent.

Pre-intervention procedures

A low-dose step-up protocol was used in all women. Daily subcutaneous injection of 75 IU of recombinant follicle-stimulating hormone (rFSH) was started on day 3 on the menstrual cycle. On the seventh day, US was performed. If the US image showed ≥ ten mm follicular development, patients were followed-up without changing dosage until one or two follicles reached a diameter of 17-20 mm. If the US image showed < ten mm follicular development, dose of rFSH was increased to 112.5 IU/day on the eighth day and the patients were followed-up with every one to three days intervals until one or two follicle reached to 17-20 mm in diameter. Subsequent dose augmentation was performed with 37.5 IU per week (up to 225 IU/day). The duration of treatment was 28-35 days. IUI was carried out 36 hours after hCG injection. A maximum of three cycles were carried out in all women.

The aim of stimulation was to achieve a mono-follicular response. In the study, IUI was also applied to women who developed double follicles. After one or two follicles with 17-20 mm in a diameter were detected sonographically, 250 μg of recombinant human chorionic gonadotropin (rhCG) was administered subcutaneously.

If three or more mature follicles (≥ 17 mm) developed or there was no follicular development, IUI was cancelled due to legal restriction for IUI. IUI of 12, six, and two women in the USG group, and 11, five, and three women in the NUSG group were cancelled at first, second, and third cycle, respectively. No OHSS was observed, because IUI was cancelled when women had three or more mature follicles (≥ 17 mm). The authors assessed endometrial thickness (ET) which reflects estrogen level at the β-hCG day. All ETs were ≥ eight mm. Three couples underwent an unplanned course of four cycles of IUI, although a maximum of three cycles were planned. One patient in the USG group and two patients in NUSG group underwent four cycles of IUI. The USG group included 64 couples treated for 99 cycles, and the NUSG group included 66 couples treated for 104 cycles.

Intervention procedures

All the patients had full bladders during IUI and the procedure was performed using the identical catheters in both groups. The catheters had a rigid outer channel and a flexible inner channel. The authors carried out one single insemination per treatment cycle 36 hours after hCG injection. All IUI procedures were performed by the same two gynecologists.

During IUI procedure in USG group, the internal flexible catheter was put into the cervical canal and passed through the internal cervical orifice. The inner catheter channel was pushed forward into the uterine cavity under abdominal US guidance until it reached within one to 1.5 cm of uterine fundus. Hence, the catheter was prevented from getting in touch with the fundus. When the flexible inner sheath did not pass through the cervical canal, the rigid outer channel was firstly passed through the cervical canal and then the IUI procedure was preceded as described above. Outer sheaths were used in three patients from each group. When it was indubitable that the catheter was in place, sperm collected in the Andrology Laboratory, by the swim-up method, were injected into the uterine cavity. It was difficult to pass the cervical canal in some patients. Abdominal ultrasound was performed using an ultrasound unit with a 3.5-MHz abdominal probe.

In NUSG group, the catheter's inner channel was pushed into the uterine cavity until the resistance of the internal cervical orifice was passed. The catheter was pushed forward two to 2.5 cm into the uterine cavity after passing the internal cervical os. If the flexible inner sheath could not pass the cervical canal, the cervical canal was passed using the rigid outer channel and the process was continued as described above. When it was thought that the catheter was in place, sperm prepared using the swim-up method in the Andrology Laboratory was introduced into the uterine cavity.

Post-intervention procedures

After the procedure, the women in both groups were advised to rest in bed for 20 minutes. No cervical tenaculum or hysterometer was used in any cases during the procedure. The β-hCG levels were measured 12 days after IUI. Pregnancy was confirmed by transvaginal US ten days after the β-hCG was positive.

Statistical Analysis

All the statistical calculations were performed with the Statistical Package for Social Sciences (SPSS) statistical software package. The number of women to be recruited was determined using a sample size calculation, and was based upon the primary outcome measure of PR per cycle. Assuming a per cycle PR of 16.8% (on the basis of the study conducted by Ramón *et al*. [15], 98 cycles in each group would be needed to detect a 17% difference between the groups (α=0.05 and power [1-β]=0.8). risk in a bilateral contrast; employing the arcsin calculation method.

The present authors used the Shapiro Wilk test to test variables for normality. Results of descriptive analysis were presented as median (minimum-maximum) and percentage. Mann Whitney U test for continuous data and Fisher's Exact test, Yates Chi-Square test and Pearson Chi-Square test for categorical data were used for comparisons between the USG and the NUSG groups. Odds ratios (OR) with 95% confidence interval (CI) were calculated for pregnancy rates (PR).

In all statistical comparisons, a p value ≤ 0.05 was used to indicate a significant difference.

Results

A total of 203 stimulated cycles in 130 patients were included. For each peer, the partner's sperms were used. USG group included 64 women and NUSG group 66. Ninety-nine cycles in USG group and 104 cycles in NUSG group were carried out.

Baseline and pre-intervention clinical characteristics of the study groups are shown in Table 1. The study groups were similar in terms of age (p = 0.710) and BMI (p = 0.631). There were no differences between the groups in any of baseline outcomes including duration of infertility (p = 0.636), total motile sperm counts (p = 0.531), basal FSH levels (p = 0.227), and rates of infertility types (p > 0.050 for all infertility factors). There were no differences between the groups in number of cycles (p = 0.448), cumulative dose of rFSH (p = 0.088) and number of follicle ≥ 17 mm (p = 0.299) as pre-intervention outcomes (Table 1).

Table 1. — *Baseline and pre-intervention clinical characteristics of the study groups.*

	USG Group (n=64)	NUSG Group (n=66)	
Number of cycles	*99*	*104*	
Age (years)[a]	28 (22-38)	28 (21-38)	0.710*
BMI (kg/m^2)[a]	25 (18-35)	25.25 (19-33)	0.631*
Duration of infertility (years)[a]	5 (1-16)	5 (2-18)	0.636*
Total motile sperm count (millions)[a]	60 (5.1-33)	57 (5.2-220)	0.531*
Basal FSH (IU/L)[a]	5.30 (2.7-10.3)	5.65 (1-11.9)	0.227*
Number of cycles[a]	1 (1-3)	1 (1-3)	0.448*
Cumulative dose of rFSH (IU)[a] †	637.50 (150-2700)	675 (262.5-2587.5)	0.088*
Number of follicles ≥17 mm[a] †	1 (1-2)	1 (1-2)	0.299*
Type of Infertility			
Mild male factor[b]	11 (17.2)	11 (16.7)	1.000***
Anovulatory[b]	13 (20.3)	18 (27.3)	0.468***
Idiopathic infertility[b]	40 (62.5)	37 (56.1)	0.455****

[a] Values are medians (minimum-maximum); [b] Values are number of cases (percentage); *Mann Whitney U Test; **Fisher's Exact Test; ***Yates Chi-Square Test; ****Pearson Chi-Square Test; †Per cycle.
Abbreviations: BMI, body mass index; FSH, follicle stimulating hormone; rFSH, recombinant follicle stimulating hormone; IU, international unit; mm, millimeter.

Table 2. — *Pregnancy rates (PR) of the study groups.*

	USG Group (n=64)	NUSG Group (n=66)	OR	95% CI	p
Per cycle PR	16/99 (16.2)	13/104 (12.5)	1.35	0.61-2.97	0.548**
First cycle PR	12/64 (18.8)	9/66 (13.6)	1.36	0.49-3.96	0.580**
Second cycle PR	3/35 (8.6)	3/37 (8.1)	1.06	0.23-4.92	1.000*
Third cycle PR	1/11 (9.1)	1/15 (6.7)	1.40	0.78-25.14	1.000*
Per woman PR	16/64 (25)	13/66 (19.7)	1.26	0.52-3.12	0.606**
Multiple PR	1/16 (6.3)	1/13 (7.7)	0.82	0.01-68.63	1.000*
Chemical PR	3/16 (18.8)	1/13 (7.7)	2.77	0.25-30.38	0.606*
Abortion	3/16 (18.8)	1/13 (7.7)	2.77	0.25-30.38	0.606*
Ongoing PR	10/16 (62.5)	11/13 (84.6)	0.30	0.05-1.86	0.238*

Values are number of cases/total (percentage); *Fisher's Exact Test; **Yates Chi-Square Test.
Abbreviations: PR, pregnancy rates; OR, odds ratio; CI, confidence interval.

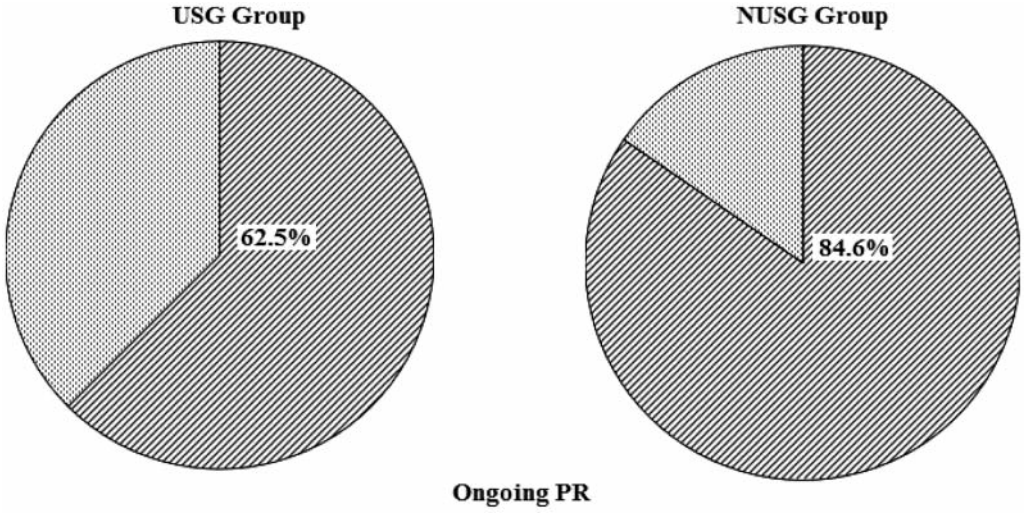

Figure 2. — Ongoing pregnancy rates of the groups.

Pregnancy rates are shown in Table 2. The PR per cycle was 16.2 % (16/99) and 12.5% (13/104) in the USG and NUSG groups, respectively. There was no difference between the groups in terms of PR per cycle (odds ratio [OR]=1.35; 95% confidence interval [95% CI]: 0.61-2.97; p=548). The first cycles PR were 18.8 % (12/64) in the USG group and 13.6% (9/66) in the NUSG group. There was no difference between the groups in first cycle PR (OR=1.06; 95% CI: 0.23-4.92; p = 1.000). There was no difference between the groups in second (OR=1.36; 95% CI: 0.49-3.96; p = 0.580) and third cycle PR (OR=1.40; 95% CI: 0.78-25.14; p =1.000). There was no difference between the groups in ongoing PR (OR= 0.30; 95% CI: 0.05-1.86; p = 0.238) (Figure 2). The PR per woman was 25% (16/64) in the USG group and 19.7% (13/66) in the NUSG groups. There was no difference between the groups in PR per woman (OR=1.26; 95% CI; 0.52-3.12; p = 0.606). The ongoing PR was 62.5% (10/16) in the USG groups and 84.6% (11/13) in the NUSG groups (Figure 2).

Abortion rates (OR=0.82; 95% CI: 0.01-68.63; p = 1.000), chemical PR (OR=0.82; 95% CI: 0.01-68.63; p = 1.000) and multiple PR (OR=1.91; 95% CI: 0.17-137.64; p = 0.606) of the groups were similar.

Discussion

The combination of controlled ovarian hyperstimulation (COH) with IUI is an important option in infertility treatment. IUI is similar to the embryo transfer procedure in IVF. Several authors have studied the factors affecting implantation rate in the embryo transfer procedure. For example, the presence of blood on the catheter is associated with a lower implantation rate [16]. US guidance in embryo transfer significantly increases the pregnancy and implantation rates in IVF [8]. The use of abdominal US during transfer avoids catheter trauma to the endometrium and decreases the damage via direct visualization of the catheter, thereby decreasing uterine contraction.

Although in recent years plenty of studies regarding to embryo transfer technique and US guided embryo transfer had been made, there is few studies dealing with the insemination technique in IUI procedure. These studies are about tenaculum, bougie, and hard catheter usage [17], but there are only two studies corresponding to USG IUI [15,19]. The embryo transfer and IUI techniques are similar in that both require cervical catheterization and release material into the endometrial cavity. Using USG during the embryo transfer procedure in IVF has been studied in detail. It is generally agreed that USG increases the pregnancy rate, although one study indicated that the pregnancy rate did not increase with USG during the embryo transfer procedure [16]. Therefore, USG during IUI should theoretically improve the pregnancy rate in controlled ovarian hyper stimulation with IUI cycles. The present authors tested this hypothesis using a methodology similar to that used by Ramón *et al*. [15], although they differed in the COH protocol and follicle limits used.

In the present study, the authors aimed for monofollicular development. A low-dose step-up protocol was used in COH, starting with 75 IU rFSH daily on day 3. Ramón *et al*. started on day 2 and administered 150 IU rFSH and one subcutaneous dose of 0.25 mg cetrorelix daily after one follicle had a diameter of 16 – 20 mm. They added 75 IU/day of recombinant luteinizing hormone (rLH) to the FSH stimulation protocol from the start of antagonist administration.

The present authors believe that Ramón *et al.* [15] had used cetrorelix for synchronizing high number of follicles formed by high dose FSH. However in a low dose step up protocol, there is no need for such an effort they did not use cetrorelix or rLH. IUI was cancelled if three or more follicles developed and they were excluded from the study since ratio of multiple pregnancy increase in these patients [18], while Ramón *et al*. [15] used five follicles as the cycle limit.

The need for tenaculum is extremely rare. Although tenaculum use does not affect pregnancy ratios, the present authors did not use it as Ramón *et al.* did [15]. They had no difficult IUI case (tenaculum, hysterometry, need for bougie). They needed to use rigid outer channel of the catheter in three patients in each group. Since there is no difference between soft and firm catheters in terms of pregnancy results [18], these cases were not evaluated as difficult IUI.

The pregnancy rates per cycle in the USG IUI 16.2% (16/99) and classical IUI 12.5% (13/104) groups were similar to those in the study reported by Ramón *et al*. (16.0%, 17/106 *vs*. 16.8%, 21/125, respectively) [15]. The pregnancy rates per woman in the present study were low compared to those reported by Ramón *et al*. for both USG IUI and classical IUI (25% and 19.7% *vs*. 51.5% and 52.5%, respectively). These differences were likely due to the differences in the cycle cancellation criterion and the number of ovulation induction cycles per woman. The rates of multiple pregnancies in the present study (6.3% (1/16) in the USG IUI and 7.7% (1/13) in classical IUI) were low compared to that reported by Ramón *et al*. [15] but the abortion rates were similar in both studies.

In contrast with the study done by Ramón *et al.* [15], recently published trial done by Oztekin *et al.* indicates there might be an increase in the pregnancy rates with the IUI procedure under US guidance [18]. Through this retrospective study, randomization was provided with applying IUI under US guidance to those patients who had a full bladder, and blindly IUI application to those who had an empty bladder. Tenaculum usage was defined as hard IUI. The pregnancy rates of the groups US used and blind IUI are reported as 23.4 (34/145), 13.9 (17/122), respectively. Difficult IUI rates were 9.7 (14/145) in the US used group and 26.2 (32/122) in the blind IUI group. A statically significant difference (p < 0.001) was determined between the hard IUIs. Although using a tenaculum infers a hard IUI, there have been studies that show there is no significant change with the pregnancy rates [11, 12]. All the patients were with a full bladder at the very beginning of the present study. Tenaculum usage was not needed at all. The present authors defined the cases as difficult IUI where we used the outer rigid outer channel of the catheter. In both groups there were only three cases where they used that rigid outer channel, so that there was no statistical difference. The present authors can relate the lack of difference between the groups to the following: uterine fundus is not touched also in the NUSG group; the uterine contractions observed in both groups are probably similar and their effects on pregnancy is equal; uterine contractions do not decrease pregnancy ratios as in embryo transfer.

Conclusion

In conclusion, the present results suggested that routine US guidance during the IUI procedure is not essential, as

routine US does not increase pregnancy rate. The present results suggest a routine US guidance during IUI is not essential as it does not increase pregnancy rates but it can be used in such cases to overwhelm some sort of difficulties.

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