



Original Article

The impact of the modified speculum application technique on the success rates of intrauterine insemination: A randomized controlled study

Ilknur Mutlu^{a,*}, Mehmet Erdem^b, Ahmet Erdem^b^a IVF Unit, NovaArt IVF and Women Health Center, Ankara, Turkey^b Department of Obstetrics & Gynaecology, Gazi University Medical School, Ankara, Turkey

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ABSTRACT

Objective: Intrauterine insemination (IUI) is frequently used to treat patients with ovulation disorders, cervical factor, mild male infertility and unexplained infertility. The aim of this study was to investigate the impact of modified speculum application on the success of IUI in patients with unexplained infertility.**Materials and methods:** This prospective randomized study reviewed 219 women who had undergone controlled ovarian hyperstimulation (COH)-IUI treatment. In the modified speculum application group (109 patients with 124 cycles), the screw of the vaginal speculum was loosened after passing the internal os with catheter and the vaginal speculum remained in this position to ensure closure of the cervix during the procedure. In the conventional speculum application group (110 patients with 132 cycles), the screw of the vaginal speculum was not loosened to close the lips of cervix after passing the internal os with the catheter and the vaginal speculum was removed after withdrawal of the insemination catheter. The primary outcome was live birth rate.**Results:** The modified and conventional speculum application groups had statistically similar demographic and clinical characteristics. There were no significant differences between the study and the control groups in terms of the clinical pregnancy rate per cycle and per patient (24.1% vs 18.9% and 26.6% vs 22.7%, respectively), as well as the live birth rate per cycle and per patient (19.3% vs 15.1% and 22% vs 18.1% respectively).**Conclusion:** Applying gentle mechanical pressure on the portio vaginalis of the cervix using a vaginal speculum during IUI does not improve pregnancy and live birth rates in patients with unexplained infertility.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Intrauterine insemination (IUI) is frequently used as a first step treatment in patients with ovulation disorders, cervical factor, mild male infertility and unexplained infertility, since it is a less invasive and less expensive procedure than in vitro fertilization (IVF) [1–3]. It simply consists of two steps: the preparation of semen in the laboratory and insertion into the uterine cavity through a catheter at the time of ovulation, which is detected by ultrasound or pre-ovulatory increase in luteinizing hormone in blood or urine. IUI

can be combined with controlled ovarian hyperstimulation (COH) and ovulation induction with human chorionic gonadotropin (hCG) for accurate timing [3].

Bypassing the cervix with an insemination catheter allows an increased number of motile and morphologically normal spermatozoa to reach the fertilization site. However, passing the catheter through the internal cervical os may induce the release of prostaglandins and trigger reflex uterine contractions [4,5]. It was shown that uterine contractions at the time of embryo transfer alter the pregnancy rates after in-vitro fertilization [6,7]. Poindexter et al. demonstrated the expulsion of 15% of the transferred embryos after embryo transfer (ET) [8]. Similarly, a considerable number of spermatozoa face the risk of being expelled out of the uterine cavity after IUI. Applying gentle mechanical pressure on the portio

* Corresponding author. IVF Unit, Novaart IVF and Women Health Center, Cukurambar Ankara, Turkey.

E-mail address: ilknurselvimutlu@hotmail.com (I. Mutlu).

vaginalis of the cervix using the vaginal speculum was investigated as an attempt to prevent embryo expulsion during and after ET. The clinical pregnancy and implantation rates were significantly improved in the speculum-closed group during ET [9].

In the current literature, several studies have examined the prognostic factors for IUI outcomes; however, the technique for speculum application during and after IUI has not yet been investigated. For this reason, we designed a prospective randomized study to explore whether modifying the IUI technique to prevent expulsion of the spermatozoa out of the uterine cavity during and after IUI could improve the success rates in patients with unexplained infertility.

Materials and methods

This study was approved by the local ethics committee and institutional review board of the study center where it was undertaken between September 2016 and September 2018. A written informed consent was obtained from each participant.

A total of 567 patients who had received COH-IUI treatment due to unexplained infertility were determined to be eligible. Unexplained infertility was diagnosed after a complete evaluation that confirmed the patency of the fallopian tubes with hysterosalpingography (HSG) or laparoscopy, an ovulatory menstrual cycle with mid-luteal progesterone levels of >3 ng/ml, basal FSH levels of ≤ 15 IU/l and normal sperm parameters according to the 2010 criteria of the World Health Organization (WHO).

At the time of IUI, 226 patients who fulfilled the inclusion criteria were offered to participate in the study. The inclusion criteria were: failure to conceive for a period of 12–60 months despite unprotected intercourse and female age between 25 and 38 years with regular menstrual cycles. Patients with polycystic ovary syndrome (PCOS), abnormal thyroid and prolactin hormone levels, hypogonadotropic hypogonadism, prior ovarian surgery, moderate/severe endometriosis and persistent ovarian cysts were excluded from the study.

After exclusion of seven patients who refused randomization, 219 patients with unexplained infertility undergoing a total of 256 COH-IUI cycles were randomized to the modified speculum application group (109 patients on 124 cycles) and the conventional speculum application group (110 patients on 132 cycles) using computer generated random number list for two consecutive treatment cycles within a period of 12 months. Once a patient was randomized, she remained in the same group throughout the study. The IUI technique for each patient was chosen by the laboratory staff according to the randomization table on the insemination day (Fig. 1).

In the conventional speculum application group, the IUI procedure was performed after introducing the catheter through the internal os and the screw of the vaginal speculum was not loosened to close the lips of cervix. Vaginal speculum was removed after withdrawal of the catheter (Fig. 2). In the modified speculum application group, the screw of the vaginal speculum was loosened after passing the internal os with the IUI catheter and the vaginal speculum remained in this position to ensure closure of the cervix during the insemination and for 5 min afterwards (Fig. 3).

All patients received a starting dose of 75–100 IU recombinant follicle stimulating hormone (FSH; Gonadotropin; Serono, Istanbul, Turkey and Merional®; IBSA, Istanbul, Turkey) after the baseline transvaginal ultrasonography on day 3 of the menstrual cycle to rule out preexisting ovarian cysts. The ovarian response and endometrial thickness were assessed with transvaginal ultrasonography starting from day 7–8 of the cycles. If the diameter of the leading follicle were <10 mm at the 8th day of stimulation, the dose of gonadotropin was increased by 50%. The gonadotropin dose

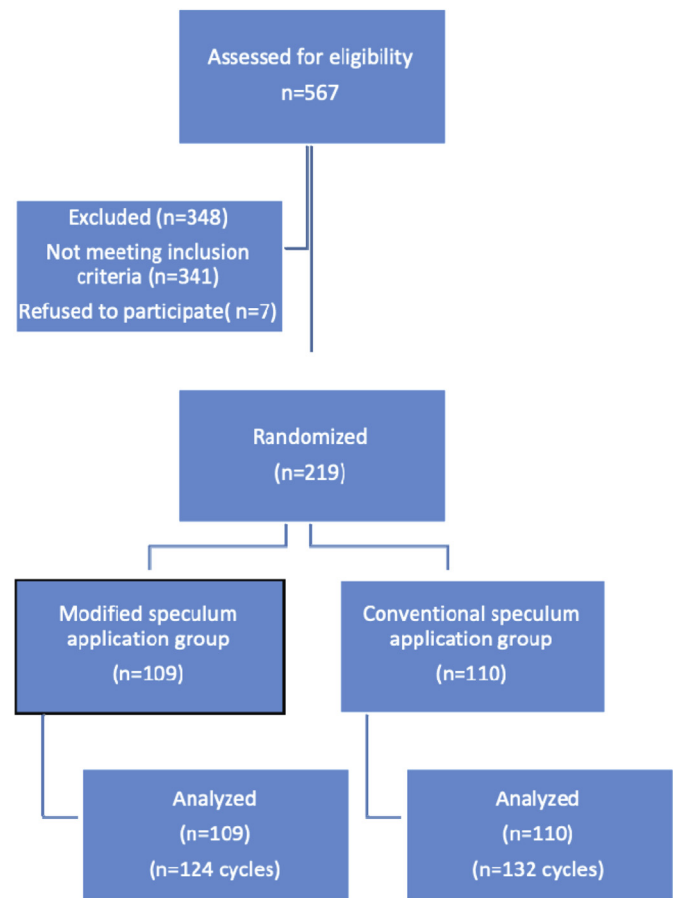


Fig. 1. The flowchart of the study design.

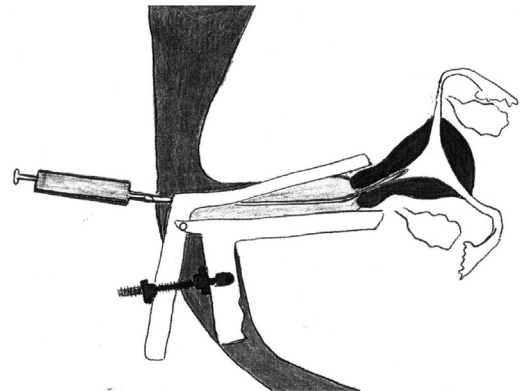


Fig. 2. Conventional speculum application techniques.

remained the same until the day of hCG trigger after the diameter of the leading follicle reached 12 mm. When at least one follicle had a diameter of ≥ 18 mm, 250 mcg hCG (Ovitrelle®; Merck Serono, Istanbul, Turkey) was administered for final maturation. The cycles with more than three dominant follicles and/or estradiol levels >1500 pg/ml were cancelled to avoid ovarian hyperstimulation syndrome (OHSS) and high-order multiple pregnancy. Each participant had a maximum of two treatment cycles. None of the patients developed moderate or severe OHSS in either of the two groups.

Semen samples were obtained through masturbation and collected in sterile containers. After liquefaction of the fresh

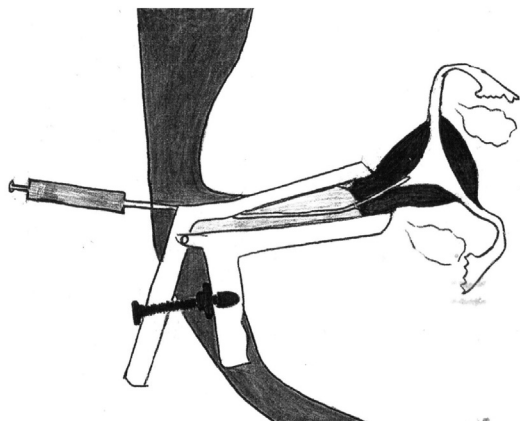


Fig. 3. Modified speculum application techniques.

ejaculate, the volume, concentration and motility were assessed according to the WHO criteria [10]. The gradient method was used in all patients using Sperm Grad-125 (Vitrolife, Sweden). Single IUI was performed 36 h after hCG administration with a disposable IUI catheter (Insemi™-Cath; Cook Medical, Bloomington, USA) by two of the authors. All patients rested in the supine position for 15 min after the procedure. For luteal support, 90 mg daily intravaginal progesterone gel (8% Crinone gel®; Merck–Serono, Istanbul, Turkey) was administered starting on the day after insemination. If the pregnancy test performed 14 days after IUI were positive, luteal support was continued until the 9th week of gestation. Pregnancy testing was performed through measurement of the serum β -hCG level on 14 days after IUI, and intrauterine pregnancy was confirmed using transvaginal ultrasonography two weeks after a positive pregnancy test. Clinical pregnancy was defined by the presence of fetal heart activity on transvaginal ultrasound. Live birth rate was defined as delivery of a living child after 24 weeks of gestation.

The primary outcome was live birth rate and the secondary outcome was clinical pregnancy rate. The sample size was computed at the beginning of the study by an online analyzer (<http://clincalc.com/Stats/SampleSize.aspx>). For an expected difference of 15% between the two groups (10% vs 25%) with 5% level of significance and a power of 80%, a total of 200 patients (100 patients per group) were required. All statistical analyses were performed using the Statistical Package for Social Sciences version 20 (SPSS, SPSS IBM, Armonk, NY, USA). The Student's t-test was used for continuous variables and the chi-square test was used for categorical variables. P values of <0.05 were considered to be statistically significant.

Results

The baseline characteristics of the modified and conventional speculum application groups have been presented in Table 1. The

groups were similar with respect to age, body mass index (BMI), duration of infertility and frequency of primary infertility. Furthermore, there were no significant differences between the study and the control groups with regard to the treatment duration, total gonadotropin dose, follicle numbers, endometrial thickness on the day of hCG and sperm parameters (Table 2).

Fifty-five clinical pregnancies were observed; 30 of these were in the modified application group and 25 were in the conventional application group. The clinical pregnancy rate per cycle (24.1% vs 18.9%), the clinical pregnancy rate per patient (26.6% vs 22.7%), the live birth rate per cycle (19.3% vs 15.1%) and the live birth rate per patient (22% vs 18.1%) were similar between the modified and the conventional application groups (Table 2). There were 6 abortions in the modified application group and 5 abortions in the conventional application group (20% vs 20%, $p > 0.05$). There were two twins and one triplet in the modified application group, while there were four twins in the conventional application group.

Discussion

The success of IUI depends on several factors including age, infertility duration, sperm morphology, the number of progressively motile spermatozoa and cycle characteristics such as ovarian stimulation protocol, the number of growing follicles, endometrial thickness and the dose of gonadotropins [1,2,11–15]. Beside the cycle and patient characteristics, the effects of catheter type and subsequent bed rest on the success of IUI have been investigated [2,16–20]. This study aimed to examine the impact of the modified speculum application technique on the success of IUI procedures.

As known, stimulation of the cervix and administration of the catheter through the internal cervical os induces the release of prostaglandins and oxytocin, which consequently trigger uterine contractions [4,5,9]. These contractions may cause immediate or delayed expulsion of embryos towards the cervical canal after embryo transfer [7,21–24]. Mansour et al. designed a prospective randomized study in which they investigated the effect of applying gentle mechanical pressure on the anterior and posterior lips of the cervix by closing the vaginal speculum and, thus, obstructing cervical canal to prevent the expulsion of transferred embryos. The results showed significantly improved clinical pregnancy rates (67.4% vs 47.8%) and implantation rates (33.3% vs 21.5%) in the speculum retention group when compared with the control group [9]. Due to the relatively large and immobile structure of the embryo and smaller quantity of transferred fluid [16], obstructing the cervical canal with vaginal speculum can be helpful in ET. On the other hand, Amui et al. did not report a significant difference in the clinical and viable pregnancy rates in women undergoing day 3 embryo transfer by means of the speculum retention technique (48.9% vs 44.4% and 43.8% vs 37.5% respectively). Such discrepancy has been attributed to the variations in the clinical characteristics of the reviewed patients [25].

As in the case of ET, insertion of a catheter through the cervical canal may also stimulate the release of prostaglandins, which

Table 1
Basal characteristics of the modified and conventional speculum application groups.

	Modified application group (n = 109)	Conventional application group (n = 110)	P value
Age (years)	30.8 \pm 4.6	31.0 \pm 4.5	NS
Body mass index (kg/m ²)	24.5 \pm 3.4	23.8 \pm 3.6	NS
Duration of infertility (years)	3.1 \pm 1.5	3.2 \pm 1.7	NS
Primary infertility (%)	85 (78.1%)	94 (84.6%)	NS
Number of IUI cycles per couple	1.1 \pm 0.4	1.1 \pm 0.36	NS

NS: Non-significant.

Table 2

Cycle characteristics of the modified and conventional speculum application groups.

	Modified application group (n = 109)	Conventional application group (n = 110)	P value
Duration of stimulation (days)	18.1 ± 81.3	18.1 ± 85.07	NS
Total gonadotropin dose (IU)	968.2 ± 384.0	873.1 ± 348.0	NS
Follicles ≥18 mm on the day of hCG (mm)	1.1 ± 0.4	1.07 ± 0.26	NS
Follicles of 14–18 mm on the day of hCG (mm)	0.98 ± 0.98	1.43 ± 2.64	NS
Endometrial thickness on the day of hCG (mm)	10.5 ± 1.61	10.0 ± 1.2	NS
Basal sperm concentration (x10 ⁶ /ml)	41.2 ± 21.9	35.3 ± 18.1	NS
Basal TPMSC (x10 ⁶ /ml)	17.8 ± 12.7	16.5 ± 12.8	NS
Basal sperm motility (%)	53.8 ± 6.3	51.4 ± 7.7	NS
Inseminated TPMSC (x10 ⁶ /ml)	14.8 ± 11.7	13.5 ± 12.4	NS
Clinical pregnancy rate per cycle (%)	30/124 (24.1%)	25/132 (18.9%)	NS
Clinical pregnancy rate per patient (%)	29/109 (26.6%)	25/110 (22.7%)	NS
Live birth rate per cycle (%)	24/124 (19.3%)	20/132 (15.1%)	NS
Live birth rate per patient (%)	24/109 (22%)	20/110 (18.1%)	NS

NS: Non-significant; TPMSC: Total progressively motile sperm count.

invokes uterine contractions in the IUI procedure. Therefore, it would be prudent to assume that vaginal speculum may be applied to obstruct the cervical canal and, thus, prevent the expulsion of inseminated spermatozoa. However, we failed to detect any significant differences between the conventional and the modified speculum application techniques with respect to clinical pregnancy and live birth rates. This failure may be due to the properties of spermatozoa and the amount of the inseminated fluid. Spermatozoa are small and mobile cells and inseminated fluid contains millions of spermatozoa. It has been shown that sperms reach fallopian tubes only a few minutes after intercourse or intrauterine insemination [26]. That is, spermatozoa can survive exhausting uterine contractions and expulsion by virtue of this progressively motile property. Furthermore, it has been shown that sperm is directed to oocyte by mechanical mechanisms (uterine contraction) towards the fundus and sensory mechanisms (thermotaxis and chemotaxis) [27]. In addition, the last review about immobilization versus immediate mobilization after intrauterine insemination showed that there was no benefit of bed rest on pregnancy rates and this finding supported these scientific data [20].

In our study, the power of the represented findings is limited by the relatively small cohort size. The low number of participants involved in the study may have obscured the potential effects of this new technique on CPR or LBR due to the inherent low pregnancy rate by IUI compared to IVF. Since one can observe the trends, though not statistically significant, of higher CPR and LBR in the study group when compared to those of the control group, a higher number of patients may change the results. Another power limiting factor is the investigation of patients with unexplained infertility in this study. As described, the modified speculum application technique may have been more effective in patients with mild male factor than patients with unexplained infertility. The rationale behind this hypothesis is that the modified speculum application technique can be addressed as an attempt for increasing the number of progressively motile spermatozoa near the fertilization site. Moreover, the duration of the modified speculum application technique was restricted to five minutes after completion of the IUI procedure. Such a restriction aimed to increase the patient compatibility by avoiding any discomfort and complaints related to the modified application technique. It may be considered that prolongation of the modified application technique may somehow lead to an improvement in clinical pregnancy and live birth rates.

In conclusion, this study has investigated the impact of a modified technique for speculum application on the success of IUI, but it has been unable to detect a significant improvement in clinical outcomes. However, this inability may be attributed to the relatively small cohort size, inclusion of patients with unexplained infertility within the study cohort and the duration of the modified

technique. Further research is warranted to explore the effects of this modified speculum application technique for IUI procedure.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgment

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