TÜBİTAK

Original Article

Turk J Med Sci
2011; 41 (5): 801-808
© TÜBİTAK
E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1009-1101

A comparison of intravenous general anesthesia and paracervical block for in vitro fertilization: effects on oocytes using the transvaginal technique

Sevil BÜMEN[1], İlkben GÜNÜŞEN[1], Vicdan FIRAT[1], Semra KARAMAN[1], Ayşin AKDOĞAN[2], Ege Nazan TAVMERGEN GÖKER[2]

Aim: To compare the effects of 2 different anesthetic techniques used for oocyte retrieval. Comparison was made based on the number of retrieved and fertilized oocytes, metaphase 2 (M2, mature) oocytes, and transferred embryos, as well as fertilization, pregnancy, and live birth rates. Ultrasound-guided transvaginal oocyte retrieval for in vitro fertilization is one of the most common minor surgical procedures. Despite this, it is stressful and painful for the patient; most patients request sedation and/or pain relief. Propofol, which is frequently used for general anesthesia in such procedures, has been suspected to damage oocytes.

Materials and methods: Results from 70 patients without premedication were compared in this randomized prospective study. Patients were divided into 2 groups based on treatment. Those in Group G received intravenous general anesthesia with atropine (10 μg kg^{-1}), remifentanil (1 μg kg^{-1}), and propofol (2.5 mg kg^{-1}), while patients in Group P received a paracervical block with 100 mg of prilocaine (2%) and 0.75 mg kg^{-1} of intramuscular meperidine.

Results: Our results revealed no statistically significant difference between the 2 groups in terms of the fertilization rate. The numbers of retrieved and mature oocytes and transferred embryos and the pregnancy rate were greater in the general anesthesia group, although only the number of transferred embryos showed a statistically significant difference ($P = 0.045$).

Conclusion: According to our data, both anesthesia techniques can be used for oocyte retrieval since there were no differences in fertilization, pregnancy, or live birth rates between the 2 groups.

Key words: General anesthesia, paracervical block, oocyte, fertilization rate, pregnancy

İnvitro fertilizasyonda intravenöz genel anestezinin transvaginal ponksiyonla alınan oositler üzerine etkilerinin paraservikal lokal anestezik blokla karşılaştırılması

Amaç: İn vitro fertilizasyonda ultrason eşliğinde transvaginal yolla oosit toplanması, en yaygın minör cerrahi girişimlerden birisidir. Bu işlem, hasta için stresli ve ağrılı olabileceğinden sedasyon ve/veya analjezi gerekir. Genel anestezi uygulamalarında sık kullanılan ilaçlardan olan propofolün oositlere zarar verebileceğinden şüphe edilmektedir. Bu çalışmanın amacı, oosit toplanması işleminde kullanılan 2 farklı anestezi tekniğinin oosit, embriyo kalitesi, fertilizasyon, gebelik ve canlı doğum oranları üzerine olan etkilerinin karşılaştırılmasıdır.

Yöntem ve gereç: Randomize, prospektif olarak yapılan bu çalışmada, premedikasyon uygulanmayan 70 hastada intravenöz genel anestezi (10 μg kg^{-1} atropin, 1 μg kg^{-1} remifentanil ve 2,5 mg kg^{-1} propofol) ile paraservikal bloğu (100 mg % 2 prilokain ve 0,75 mg kg^{-1} intramüsküler meperidin) karşılaştırdık.

Received: 06.09.2010 – Accepted: 22.11.2010

[1] Department of Anesthesiology and Reanimation, Faculty of Medicine, Ege University İzmir - TURKEY
[2] Family Planning-Infertility Research and Treatment Center, Ege University, İzmir - TURKEY
Correspondence: *İlkben GÜNÜŞEN, Department of Anesthesiology and Reanimation, Faculty of Medicine, Ege University, İzmir - TURKEY*
E-mail: ilkben.gunusen@ege.edu.tr

Bulgular: Fertilizasyon oranları açısından 2 grup arasında istatistiksel bir fark saptanmadı. İşlem sonrası elde edilen oosit ve matür oosit sayısı ile transfer edilen embriyo sayısı ve gebelik oranları genel anestezi grubunda daha iyi bulunmasına karşın, istatistiksel farklılık sadece transfer edilen embriyo sayısında saptandı (P = 0,045).

Sonuç: Elde ettiğimiz verilere göre, her 2 grup arasında fertilizasyon, gebelik, canlı doğum oranları açısından istatistiksel bir fark saptanmadığından, her 2 anestezi tekniğinin de oosit toplanması işlemi için kullanılabileceği düşüncesindeyiz.

Anahtar sözcükler: Genel anestezi, paraservikal blok, oosit, fertilizasyon oranı, gebelik

Introduction

Oocyte retrieval is one of the most vital aspects of in vitro fertilization (IVF). The process of IVF requires the harvesting of mature oocytes from the ovaries of infertile patients. These oocytes are subsequently fertilized in vitro and allowed to develop into embryos that are finally transferred into the uterus of these patients. Great efforts have been made to make the procedure as safe and comfortable as possible for the patient. Adequate pain control is of paramount importance, not only for the patient's comfort but also because it can facilitate the process of follicular puncture and decrease the chance of trauma to adjacent organs (1,2). Patients undergoing in vitro fertilization may be exposed to various techniques of anesthesia (3). Different options include general anesthesia, neuraxial anesthesia (epidural or spinal), conscious sedation, or the injection of local anesthetic agents into the cervix or the vaginal wall (2). The optimal anesthetic technique should allow good surgical anesthesia with minimal side effects, a short recovery time, and, if possible, a high rate of successful pregnancy (4). General anesthesia with intravenous (IV) agents used to be the most popular form of pain control for transvaginal oocyte retrieval in assisted reproduction (5). However, it has been determined that different anesthetic agents have different effects on oocyte fertilization and embryonic development (6-9). Anesthetics like midazolam, fentanyl, alfentanil, and lidocaine in a human study (10,11) and isoflurane in an animal study (6) have been reported in follicular fluid. Vincent et al. (7) found that propofol was associated with lower clinical and ongoing pregnancy rates when compared to isoflurane. Other studies revealed no detrimental effects or negative outcomes, however (8,9).

Propofol has been widely used either alone or in combination with other agents for oocyte retrieval (2). Furthermore, remifentanil is a μ-opioid receptor agonist with an analgesic potency similar to that of fentanyl. Because of remifentanil's rapid systemic elimination, with a half-life of 8-10 min, it may have pharmacokinetic advantages in clinical situations requiring the predictable termination of effect (12). In this study, we compared the effects of both anesthesia techniques on the oocytes and outcomes in IVF cycles. The standard regimen for IVF in our institution has been either intravenous general anesthesia with propofol and remifentanil (not inhalation agents or nitrous oxide) while maintaining spontaneous ventilation, or paracervical local anesthesia with 2% prilocaine and intramuscular (IM) meperidine. We therefore designed the present study according to this standard protocol and aimed to test the hypothesis that the effects of these techniques on fertilization, pregnancy, and live birth rates would be similar.

Materials and methods

After obtaining approval from the ethics committee and written informed consent from the patients, 80 unpremedicated healthy women were included in this study. All of the patients were of American Society of Anesthesiologist (ASA) physical status I and between 25 and 40 years of age, and all had been scheduled for ultrasound-guided oocyte retrieval using the transvaginal technique. Ovulation induction was performed with a gonadotropin-releasing hormone antagonist (Cetrotide®, Serono; or Orgalutran®, Schering-Plough) and a recombinant follicle-stimulating hormone (FSH) (Puregon Pen®, Schering-Plough; or Gonal-F®, Serono). Human chorionic gonadotropin (HCG) was administered 34-36 h prior to oocyte retrieval. The oocyte retrieval procedure was performed transvaginally

under ultrasound guidance. After the aspiration of follicular fluid, the cumulus/oocyte complex was transferred to the medium. Following the removal of the cumulus cells, all oocytes were examined for maturation and mature oocytes were fertilized by the standard intracytoplasmic sperm injection (ICSI) procedure that same day. All semen samples were freshly obtained from patients' husbands by masturbation. Fertilization was assessed 18-20 h after the ICSI procedure. Embryonic development was examined during the incubation period and embryo quality was assessed by an embryologist. Top-grade embryos were transferred to the uterine cavity 48-72 h after oocyte retrieval. Vaginal progesterone gel (Crinone 8%, Serono) was given to all subjects for luteal support. Pregnancy was confirmed by serum B-HCG measurement 14 days after the embryo transfer and clinical pregnancy was confirmed by ultrasound 3 weeks after the embryo transfer. Inclusion criteria for potential subjects were a body mass index (BMI) between 19 and 24 kg/m^2, regular menstruation, and basal FSH levels lower than 10 mIU/mL, luteinizing hormone (LH) levels lower than 10 mIU/mL, and estradiol (E2) levels lower than 60 mIU/mL. Exclusion criteria for potential subjects were a history of a significant endocrine, cardiac, pulmonary, hepatic or renal disease; chronic drug or alcohol abuse; disabling neuropsychiatric disorders; morbid obesity; hypersensitivity to anesthetic drugs; or the presence of a myoma or endometrioma.

Lactated Ringer's solution was started through a 20-gauge IV cannula, which was inserted into the right hand. Using a computer-generated randomization list, patients were randomly divided in 2 groups (40 subjects per group) according to the anesthetic regimen. In the first group, Group G, general anesthesia was obtained with atropine (10 μg kg^{-1}), remifentanil (1 μg kg^{-1}), and propofol (2.5 mg kg^{-1}). In the second group, Group P, a paracervical block with 100 mg of prilocaine 2% (total volume: 10 mL, paracervical injection of 5 mL into each lateral vaginal fornix) was applied along with 0.75 mg kg^{-1} of IM meperidine. Anesthesia in Group G was maintained by repeated boluses of propofol (0.5-1 mg kg^{-1}, if necessary) and ventilation was manually assisted using a facemask with 50% oxygen/air. In this group, inhalation anesthetics were not used and patients were treated by 0.5 μg kg^{-1} of bolus remifentanil in the event of inadequate analgesia (e.g. an increase of 20% from baseline in mean blood pressure or heart rate). In the operating room, routine physiological monitoring was applied, including electrocardiogram (ECG), noninvasive blood pressure (systolic, diastolic, and mean blood pressure), heart rate (HR), and pulse oximeter (Datex-Ohmeda AS/3, Helsinki, Finland) monitoring. Transvaginal oocyte retrieval was performed using a 17-gauge needle under ultrasound guidance. When the needle was introduced into a follicle, suction of 90-100 mmHg was applied until the follicle was emptied. This process was performed for each visible follicle under ultrasound. The duration of the procedure was defined as the span of time from the initial placement of the vaginal ultrasound probe until its removal at the end of the procedure. All patients were evaluated by the same surgeon and anesthesiologist. At the end of the procedure, recovery time for the general anesthesia group was evaluated using the Aldrete score, a scale of 0-10; patients with scores ≥9 were discharged from the operating room to the postanesthesia care unit (13). The surgeon's acceptance was evaluated using a 2 point scale: the intraoperative conditions of the patient were considered satisfactory if the surgeon would utilize the same anesthetic method again, and unsatisfactory if the surgeon preferred a different method for future procedures (14). Both groups of patients were evaluated in terms of basal FSH, E2 levels, the number of retrieved and mature (M2) oocytes, the number of fertilized oocytes, and the number of transferred embryos, as well as fertilization, pregnancy and live birth rates.

Statistical analyses were made using SPSS 13.0 (Statistical Package for the Social Sciences; SPSS, Chicago, IL, USA). The results are presented as mean ± standard deviation or number (%), as appropriate. The patient's physical characteristics, IVF laboratory evaluations, and surgical times were compared using Student's t-test. Pregnancy and live birth rates were compared using a chi-square test and Fisher's exact test. Changes over time were evaluated with analysis of variance for repeated measures. All post hoc comparisons were performed using the Bonferroni correction. $P < 0.05$ was considered to be statistically significant.

Results

Initially, 80 patients were included in this investigation, but 8 patients in Group G and 2 patients in Group P were excluded from the study due to problems appearing after the oocyte retrieval. From Group G, 2 patients had ovarian hyperstimulation, 2 patients had immature oocytes, in 1 patient no oocytes were found, and for 3 patients no motile sperm was found in their husbands' ejaculate. In Group P, 1 patient experienced ovarian hyperstimulation and, therefore, no embryo transfer was performed; for another patient, no motile sperm was found in her husband's ejaculate. All of these issues were related to poor or excessive response to ovarian stimulation or to sperm problems. After excluding these patients, this study examined 70 women, 38 of whom received paracervical block and 32 of whom received general anesthesia. There were no significant differences between the groups with regard to patients' physical characteristics and surgical time (Table 1).

Both groups had similar baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and HR. In an intergroup comparison, all hemodynamic parameters (SBP, DBP, MBP, and HR) were significantly lower in Group G when compared to Group P. The comparison showed that SBP, DBP, MBP, and HR were significantly decreased in Group G at all measurement points when compared to baseline values (Table 2).

Table 1. Patient characteristics and surgical time by treatment group.

	Group G (n: 32)	**Group P** (n: 38)
Age (years)	30.6 ± 4.6	32.4 ± 4.6
Weight (kg)	63.4 ± 7.8	61.4 ± 6.6
Height (cm)	163.4 ± 7.6	163.8 ± 5.3
BMI (kg/m^2)	23.6 ± 1.3	22.8 ± 1.9
Duration of surgery (min)	11.8 ± 5.9	10.5 ± 4.7

Data are mean ± SD.
BMI: body mass index.

Table 2. Intraoperative hemodynamic changes by treatment group.

	Baseline values	**After anesthesia induction**	**End of surgery procedure**	**P-values***
HR				
Group G	94.9 ± 15.4	81.5 ± 12*	80.8 ± 9.1*	<0.0001
Group P	94.9 ± 14.7	108 ± 18.8	100.2 ± 17.8	
SBP				
Group G	111.5 ± 16	93.2 ± 112.6*†	96.2 ± 11.2*†	<0.0001
Group P	114.5 ± 14.4	117.6 ± 16.9	114.5 ± 16	
DBP				
Group G	69.6 ± 10.3	57.8 ± 10.6*†	61.3 ± 8.7*†	<0.0001
Group P	73.1 ± 10.4	72.7 ± 12.8	72.4 ± 11.9	
MBP				
Group G	84 ± 11.4	69.3 ± 10.3*†	72.3 ± 9.3*†	<0.0001
Group P	86.6 ± 10.9	87.1 ± 13.2	86.1 ± 12.8	

Data are mean ± SD.
*P < 0.05 between groups, †P < 0.05 according to baseline value in each groups.
HR: heart rate, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure, **MBP:** mean blood pressure.

The total amount of propofol was 265.6 ± 12.1 mg and the total amount of remifentanil was 115.4 ± 8.6 μg in the general anesthesia group. The recovery time was 1 or 2 min for most of the patients in this group, although it was 3 min for 5 patients and 4 min for 1 additional patient. The mean recovery time of patients in the general anesthesia group was 1.81 ± 0.8 min. The surgeon satisfaction rate was not statistically different for either group, with 87.5% of the patients in Group G and 76.3% in Group P considered satisfactory (P = 0.35).

The laboratory evaluation results of the patients are presented in Table 3. There was no difference in the FSH, LH, and estradiol levels between groups. The mean number of oocytes obtained was 11.6 ± 8.4 in the general anesthesia group while it was 8.1 ± 7 in the paracervical group, a difference that did not reach statistical significance. The number of fertilized oocytes and the fertilization rate were similar in both groups. The number of transferred embryos was statistically higher in the general anesthesia group (2.7 ± 0.6 compared to 2.4 ± 0.8, P = 0.045), while the implantation rate in both groups was similar. The pregnancy rate was 56.3% for the general anesthesia group and 44.7% in the paracervical group (P = 0.47).

The live birth rates were 31.6% (12/38) in Group P and 43.8% (14/32) in Group G; the difference was not found to be statistically significant (P = 0.32). Additionally, 1 woman from each group experienced extrauterine pregnancy, and 4 patients had miscarriages in Group P and 3 had miscarriages in Group G. There were no statistically significant differences between the groups (P > 0.05).

Discussion

In this prospective study of 2 alternatives for pain control during oocyte retrieval, we found that both anesthetic techniques had similar effects on oocytes, fertilization rate, pregnancy rate, and live birth rate. The surgeon satisfaction rate was also similar in both groups. Although the number of transferred embryos

Table 3. In vitro fertilization laboratory parameters by treatment group.

	Group G (n: 32)	**Group P** (n: 38)	**P-values**
FSH	6.7 ± 2.6	7.6 ± 3.2	0.19
LH	4.8 ± 1.8	5.5 ± 3	0.29
E2	41.5 ± 15.8	43 ± 14.4	0.69
Oocytes retrieved (n)	11.6 ± 8.4	8.1 ± 7	0.06
M2 oocytes (n)	9 ± 6.3	6.5 ± 5.5	0.09
M2/oocyte (%)	82 ± 18.1	83.4 ± 19.9	0.76
Fertilized oocytes (n)	6.4 ± 4.7	4.7 ± 3.9	0.1
Fertilization rate (%)	73.7 ± 20.1	73.4 ± 25.3	0.96
Transferred embryos (n)	2.7 ± 0.6	2.4 ± 0.8	0.045*
Implantation rate (%)	29.6 ± 30.4	26.7 ± 31	0.69
Pregnancy rate (%, n)	56.3 (18)	44.7 (17)	0.47

Data are mean ± SD, n: number.
M2: metaphase 2.
*P < 0.05 between groups.

was significantly higher in the general anesthesia group, it did not reach a clinical difference. As expected, intraoperative hemodynamic data were lower in the general anesthesia group and recovery time was usually 1 to 2 min for most patients in this group.

The results of general anesthesia using inhalation agents, nitrous oxide, intravenous agents (especially propofol), and opioid analgesics for oocyte retrieval are controversial in assisted reproduction techniques (3). Propofol is an ideal anesthetic for ambulatory surgical procedures such as ovum retrieval because it has a rapid onset, provides stable operating conditions, and offers rapid recovery after its discontinuation (15). Although propofol is frequently preferred, its use during transvaginal oocyte retrieval is currently being debated (16). An animal study reported that the use of propofol had a detrimental effect on oocyte fertilization and early embryonic development (17). However, Imoedemhe et al. (8) reported no detrimental effects or negative outcomes in human in vitro fertilization when propofol was used. Furthermore, Rosenblatt et al. (15) had no evidence from their data that the administration of propofol during the oocyte retrieval for oocyte donation had a negative impact on the oocytes as measured by the cumulative embryo scores, probability of a clinical pregnancy, or implantation rate. Christiaens et al. (16) showed that a propofol-based anesthetic technique resulted in significant concentrations of this agent in the follicular fluid, in relation to the dose administered and to the duration of propofol administration. Ben-Shlomo et al. (5), however, could demonstrate neither a correlation between the concentrations of propofol in follicular fluid and the duration of anesthesia nor a detrimental effect of high concentrations of follicular fluid propofol on oocyte quality. These authors reported that they never used a dose higher than 5 mg kg^{-1}, whereas Christiaens et al. (16) reported using doses of propofol up to 10 mg kg^{-1}. Alsalili et al. (18) evaluated the effects of different propofol concentrations (from 0.1 to 10 μg mL^{-1}) on the ability of mouse oocytes to mature in vitro. A significant reduction in maturation rates was observed in oocytes exposed to concentrations of 10 μg mL^{-1} of propofol for 30 min. However, even when exposed to the highest propofol concentrations, mature oocytes had similar fertilization and cleavage rates when compared to the controls. Although propofol concentrations in the follicular fluid are directly related to the amount administered and to the duration of administration, it does not seem to have any significant adverse effect on oocyte quality or pregnancy rates (2). When this agent is used for the induction of anesthesia only, the likelihood of a negative effect on the subsequent implantation rate may be greatly reduced, as the accumulation of propofol in the follicular fluid will be less pronounced following a single bolus administration (9). Other agents such as fentanyl, alfentanil, and midazolam have also been used either alone or in combination with propofol for oocyte retrieval. Although they tend to accumulate in the follicular fluid during anesthesia, follicular levels are very low compared with serum levels (11). So far there is limited information about the individual impact of these agents on oocyte and embryo quality; nevertheless, studies that compared different combinations of these agents have not shown them to have any significant impact (2). Hammadeh et al. (19) determined that there were no significant differences in cleavage and pregnancy rates between general anesthesia with a combination of remifentanil and either propofol or isoflurane and sedation with midazolam, diazepam, or propofol. In a study reported by Wilhelm et al. (20), pregnancy rates were significantly higher with remifentanil infusion than with general anesthesia (alfentanil, propofol, nitrous oxide, or isoflurane) in transvaginal oocyte retrieval. Moreover, Öztürk et al. (21) found that the pregnancy rate and rate of success for embryonic transfer were significantly lower in a group that had received a paracervical block plus remifentanil infusion in comparison with a group receiving a remifentanil infusion alone. The authors stated that this reduction was independent of their anesthesia technique; in both groups, remifentanil consumption was higher than in our study. We believe that the similar results found in the pregnancy and live birth rates of both groups is due to the use of low dosages of propofol and remifentanil.

Local paracervical anesthesia can provide adequate levels of analgesia during the puncture of the vaginal wall. The use of local anesthesia has been associated with good pain control only in a small fraction of well-motivated patients (2). Kaya et al. (22) demonstrated that a paracervical block with

lidocaine plus an IV remifentanil infusion provided satisfactory analgesia. There are only a few studies in the literature on the effects of using prilocaine for IVF (23,24). However, the aims of these studies were generally to determine the pain scores of patients, not to evaluate the effects on pregnancy, fertilization, or oocytes. Godoy et al. (23) compared the use of paracervical block with mepivacaine and with prilocaine. The 2 local anesthetics were both effective in reducing pain during the transvaginal oocyte retrieval. There are some studies demonstrating the effects of other local anesthetics on fertilization and embryos (25,26). Schnell et al. (25) concluded that the local anesthetics lidocaine, chloroprocaine, and bupivacaine adversely affected in vitro fertilization and embryo development in mice. Furthermore, Dell Vale et al. (26) reported that lidocaine adversely affected the in vitro development of mouse embryos. Wikland et al. (10) showed that fertilization and cleavage rates did not differ significantly in women with and without paracervical block with lidocaine, however. In addition, the pregnancy rate did not differ between the 2 groups. These researchers were able to detect lidocaine in the follicular fluid when using paracervical blocks; thus, it seems that the concentration of lidocaine found in the follicular fluid after a paracervical block with 50 mg of lidocaine does not negatively affect fertilization of the human oocyte or early cleavage of the human embryo. Furthermore, a metaanalysis that included 115 prospective studies evaluating general or locoregional anesthesia on reproductive outcomes (cleavage and pregnancy rate) for in vitro fertilization showed no statistical difference in either anesthetic technique (3). These results failed to demonstrate a correlation between human studies and animal studies (3,23,25,26). A case-control study found no differences between fertilization rates or embryo cleavage characteristics while comparing propofol-based general anesthesia and a paracervical block with mepivacaine (9). These investigators reported initial implantation and fertilization rates after propofol anesthesia similar to the rates in the local anesthetic group in our study. Hammadeh et al. (19) determined that general anesthesia seemed to improve the success rate for oocyte retrieval, a result that is most probably explained by the improved comfort for both the patient and the gynecologist during the transvaginal puncture procedure. In addition, general anesthesia enables the gynecologist to harvest even smaller follicles and thereby it especially increases the aspiration rate of smaller, immature oocytes.

Jennings et al. (27) determined that meperidine was nontoxic for oocyte recovery. Furthermore, a previous study showed that in vitro development of mouse embryos to the blastocyst stage was used to assess the toxicity of isoflurane, fentanyl, and meperidine. At concentrations similar to those employed during human oocyte recovery for IVF, isoflurane significantly inhibited mouse embryo development. However, meperidine and fentanyl did not affect IVF success (6).

A limitation of this study is that power analysis is lacking. Although we initially planned to include more patients, the number of patients undergoing general anesthesia was very low. This is due to the fact that more than 98% of the ultrasound-guided transvaginal oocyte retrieval procedures performed at our institution are conducted using a paracervical block.

Because fertilization, implantation, pregnancy, and live birth rates were similar in both groups, we believe that intravenous general anesthesia with propofol plus remifentanil had no negative effect on oocytes. In light of this, we conclude that general anesthesia may be considered as a suitable alternative to paracervical block for IVF procedures.

References

1. Yasmin E, Dresner M, Balen A. Sedation and anaesthesia for transvaginal oocyte collection: an evaluation of practice in the UK. Hum Reprod 2004; 19; 2942-5.

2. Vlahos NF, Giannakikou I, Vlachos A, Vitoratos N. Analgesia and anesthesia for reproductive technologies. Int J Gynaecol Obstet 2009; 105: 201-5.

3. Kim WO, Kil HK, Koh SO, Kim JI. Effects of general and locoregional anesthesia on reproductive outcome for in vitro fertilization: a meta-analysis. J Korean Med Sci 2000; 15: 68-72.

4. Martin R, Tsen LC, Tzeng G, Hornstein MD, Datta S. Anesthesia for in vitro fertilization: The addition of fentanyl to 1.5% lidocaine. Anesth Analg 1999; 88: 523-6.

5. Ben-Shlomo I, Moskovich R, Golan J, Eyali V, Tabak A, Shalev E. The effect of propofol anaesthesia on oocyte fertilization and early embryo quality. Hum Reprod 2000; 15: 2197-9.

6. Chetkowski RJ, Nass TE. Isoflurane inhibits early mouse embryo development in vitro. Fertil Steril 1988; 49: 171-3.

7. Vincent RD Jr, Syrop CH, Van Voorhis BJ, Chestnut DH, Sparks AE, McGrath JM et al. An evaluation of the effect of anesthetic technique on reproductive success after laparoscopic pronuclear stage transfer. Propofol/nitrous oxide versus isoflurane/nitrous oxide. Anesthesiology 1995; 82: 352-8.

8. Imoedemhe DA, Sigue AB, Abdul Ghani I, Abozeid MA, Abdel Halim MS. An evaluation of the effect of the anesthetic agent profofol (Diprivan) on the outcome of human in vitro fertilization. J Assist Reprod Genet 1992; 9: 488-91.

9. Christiaens F, Janssenswillen C, Van Steirteghem AC, Devroey P, Verborgh C, Camu F. Comparison of assisted reproductive technology performance after oocyte retrieval under general anaesthesia (propofol) versus paracervical local anaesthetic block: a case-controlled study. Hum Reprod 1998; 13: 2456-60.

10. Wikland M, Evers H, Jakobsson AH, Sandqvist U, Sjöblom P. The concentration of lidocaine in follicular fluid when used for paracervical block in a human IVF-ET programme. Hum Reprod 1990; 5: 920-3.

11. Soussis I, Boyd O, Paraschos T, Duffy S, Bower S, Troughton P et al. Follicular fluid levels of midazolam, fentanyl, and alfentanil during transvaginal oocyte retrieval. Fertil Steril 1995; 64: 1003-7.

12. Bürkle H, Dunbar S, Van Aken H. Remifentanil: a novel, short-acting, mu-opioid. Anesth Analg 1996; 83: 646-51.

13. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg 1970; 49: 924-34.

14. Casati A, Valentini G, Zangrillo A, Senatore R, Mello A, Airaghi B et al. Anaesthesia for ultrasound guided oocyte retrieval: midazolam/remifentanil versus propofol/fentanyl regimens. Eur J Anaesthesiol 1999; 16: 773-8.

15. Rosenblatt MA, Bradford CN, Bodian CA, Grunfeld L. The effect of a propofol-based sedation technique on cumulative embryo scores, clinical pregnancy rates, and implantation rates in patients undergoing embryo transfers with donor oocytes. J Clin Anesth 1997; 9: 614-7.

16. Christiaens F, Janssenswillen C, Verborgh C, Moerman I, Devroey P, Van Steirteghem A et al. Propofol concentrations in follicular fluid during general anaesthesia for transvaginal oocyte retrieval. Hum Reprod 1999; 14: 345-8.

17. Janssenswillen C, Christiaens F, Camu F, Van Steirteghem A. The effect of propofol on parthenogenetic activation, in vitro fertilization and early development of mouse oocytes. Fertil Steril 1997; 67: 769-74.

18. Alsalili M, Thornton S, Fleming S. The effect of the anaesthetic, Propofol, on in-vitro oocyte maturation, fertilization and cleavage in mice. Hum Reprod 1997; 12: 1271-4.

19. Hammadeh ME, Wilhelm W, Huppert A, Rosenbaum P, Schmidt W. Effects of general anaesthesia vs. sedation on fertilization, cleavage and pregnancy rates in an IVF program. Arch Gynecol Obstet 1999; 263: 56-9.

20. Wilhelm W, Hammadeh ME, White PF, Georg T, Fleser R, Biedler A. General anesthesia versus monitored anesthesia care with remifentanil for assisted reproductive technologies: effect on pregnancy rate. J Clin Anesth 2002; 14: 1-5.

21. Öztürk E, Günaydın B, Karabacak O, Tuncer B, Erdem M, Erdem A et al. Remifentanil infusion and Paracervical block combination versus remifentanil infusion alone during in vitro fertilization. Turk J Med Sci 2006; 36: 105-11.

22. Kaya K, Öztürk E, Tuncer B, Günaydın B. Remifentanil infusion and paracervical block combination for transvaginal ultrasound guided oocyte retrieval. Turk J Med Sci 2005; 35: 99-105.

23. Godoy H, Erard P, De Munck L, Camus M, Gepts E, Van Steirteghem AC et al. Comparison of two local anaesthetics in transvaginal ultrasound-guided oocyte retrieval. Hum Reprod 1993; 8: 1093-7.

24. Hildebrandt NB, Høst E, Mikkelsen AL. Pain experience during transvaginal aspiration of immature oocytes. Acta Obstet Gynecol Scand 2001; 80: 1043-5.

25. Schnell VL, Sacco AG, Savoy-Moore RT, Ataya KM, Moghissi KS. Effects of oocyte exposure to local anesthetics on in vitro fertilization and embryo development in the mouse. Reprod Toxicol 1992; 6: 323-7.

26. Del Valle LJ, Orihuela PA. Cleavage and development and cultured preimplantation mouse embryos exposed to lidocaine. Reprod Toxicol 1996; 10: 491-6.

27. Jennings JC, Moreland K, Peterson CM. In vitro fertilization. A review of drug therapy and clinical management. Drugs 1996; 52: 313-43.