

Anesthesia for *in vitro* fertilization

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ABSTRACT

In vitro fertilization (IVF) is one of the most recent advances in the treatment of infertility. The availability and utilization of this technology are increasing by the hour. IVF procedures are usually performed on an outpatient basis under day care surgery units. Various anesthetic modalities and analgesic regimens have been tested in different studies, but no definite conclusion so far been made regarding the preferred technique for anesthesia and pain relief for these procedures. Many anesthetic drugs have been detected in the oocyte follicular fluid and may potentially interfere with oocyte fertilization and implantation. The ideal anesthetic technique for IVF should provide good surgical anesthesia with minimal side effects, a short recovery time, high rate of successful pregnancy, and shortest required duration of exposure. The preferred method of anesthesia and analgesia should be individualized as at present there are no perfect answers.

Key words: analgesia, *in vitro* fertilization, oocyte retrieval, sedation

INTRODUCTION

Advances in medicine have greatly decreased maternal morbidity and mortality. However, this has given the gynecologist a new challenge of dealing with infertility. The most recent and advanced answer to this problem is *in vitro* fertilization (IVF).^[1,2] Started first in the late 1970s, IVF is now a reasonable answer to infertility due to both maternal and paternal disorders.^[3] As always a new surgical technique is another new challenge to the enthusiastic anesthetist. Anesthesia may be required in various aspects of the patient's treatment, which demands judicious perioperative management.

IVF techniques include:

- Ovarian stimulation and monitoring.
- Ultrasound-directed oocyte retrieval or transvaginal follicle aspiration.
- Fertilization in the laboratory and transfer of embryos back into the uterus.^[4]

General considerations

Coexisting illness

Patients may be suffering from any medical/surgical disorders.^[5-9] Special emphasis should be made on known/anticipated cause of the infection, that is, tuberculosis^[10] and thyroid disorders.^[11]

Current medications

Patients may be on anticoagulants,^[12] thyroid medications, antidepressants/anxiolytics,^[13] analgesics or antitubercular drugs.

Special considerations

Morbid obesity, severe renal/cardiac/pulmonary disease. In cancer patients, oocyte retrieval usually being performed prior to chemo/radiotherapy.^[14]

Anesthetic considerations

Oocyte retrieval was previously done laparoscopically but is now being done less invasively through the vagina.^[15,16] This process is very stressful and painful.^[17] Previously, it has been reported that due to stress there is 50 fold transient increase in serum prolactin levels during oocyte retrieval under general anesthesia (GA) which may affect IVF outcome.^[18] There may be need of repeated exposure of anesthesia for IVF till success is achieved which makes patient anxious.

Adequate pain relief is required for immobilization and eliminates the danger of piercing any vessel and for patient comfort.

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Nowadays, the IVF procedures are performed as “day care” cases and the principle of “ambulatory anesthesia” is used in these patients. Anesthetic techniques, pneumoperitoneum (if laparoscopy is required) and pharmacological agents used for IVF are the factors to be taken under considerations. These procedures should not interfere with oocyte fertilization or early embryo development and implantation.

Effect of anesthetic agents on *in vitro* fertilization techniques

Anesthetic agents have been found in the follicular fluid, and these drugs may have adverse effects on oocyte fertilization and embryonic development. Prolonged period of exposure with GA can lead to lower pregnancy and delivery rates.^[18] Pneumoperitoneum with carbon dioxide exposure during laparoscopy may have detrimental effects on oocyte quality and in combination with GA with nitrous oxide (N₂O) appear to influence fertilization and cleavage *in vitro*.^[19] But, Rosen *et al.* did not find the deleterious effect of N₂O on the rates of fertilization or pregnancy when used during an isoflurane-based general anesthetic technique.^[20] Short-acting opioids, principally fentanyl and remifentanyl, do not alter IVF success rates.^[21]

Pharmacological exposure to the anesthetic agents should be for the least possible duration with minimal penetration to follicular fluid. Assessment of specific anesthetic drugs must be interpreted with the method of administration, dose of anesthetic agents, combination with other drugs, timing of administration, and duration of exposure. For example, local anesthetic agents yield dissimilar pharmacokinetic profiles when administered via paracervical, epidural, and intrathecal techniques. Anesthetic agents may also affect unfertilized oocytes and fertilized embryos differently; thus, studies of anesthetic agents used for a (gamete *in vitro* fertilization-prefertilization) procedure should not be directly compared with studies of agents used for a (zygote *in vitro* fertilization-postfertilization) procedure. Finally, significantly higher free concentrations of certain agents (e.g., bupivacaine) exist during IVF stimulation because of a decrease in plasma protein binding capacity.^[22]

Pain during *in vitro* fertilization procedures

The pain expressed during aspiration of oocytes is identical to intensive menstrual pain and produced by the needle inserted through the vaginal wall and by mechanical stimulation of the ovary.^[17] The number of follicles and duration of the oocyte retrieval procedure may affect the pain intensity. Single follicle aspiration would take lesser time and cause less pain as compared to multiple follicle aspirations.^[23] A favorable analgesic regimen for oocyte retrieval must have no toxic effects on the oocytes with rapid onset, rapid recovery, ease of

administration, and monitoring. Most frequently opioids and benzodiazepines have been used for pain relief during IVF procedures. Although many of these agents have been found in the follicular fluid, there is a lack of clear evidence to reveal adverse effects on oocytes.

In vitro fertilization anesthesia techniques

Oocyte retrieval for IVF is usually performed transvaginally under ultrasound guidance which is a relatively brief (20 ± 30 min) outpatient procedure. It necessitates a short-acting anesthetic approach with minimal side effects. The various anesthetic modalities used for transvaginal oocyte retrieval include monitored anesthesia care, conscious sedation, GA, regional anesthesia, local injection as a paracervical block (PCB), epidural block, subarachnoid block, total intravenous anesthesia (TIVA), patient-controlled analgesia (PCA), and acupuncture. A survey conducted by Bokhari and Pollard^[24] in UK showed the use of sedation in 46% of the centers, GA in 28%, regional anesthesia with sedation in 12% while a cocktail regime was followed by the rest 14%.

Monitored anesthesia care and conscious sedation

Monitored anesthesia care (MAC) is relatively easy to deliver; drugs are well-tolerated and best suited in day care settings. It avoids the potentially harmful effects of anesthetic drugs on oocytes. Different methods of conscious sedation and analgesia have been used for oocytes recovery for IVF techniques. Drugs used for these procedures are selected by the quality of sedation and analgesia and their deleterious effects on reproductive outcomes. According to updated cochrane review conducted in 2013, the various approaches for MAC and conscious sedation used for IVF appeared to be acceptable and were associated with a high degree of satisfaction in women and it was found that simultaneous use of more than one method of sedation and analgesia resulted in better pain relief than one modality alone.^[17] The optimal method should be individualized based on the preferences of both the women and the clinicians and resource availability. The various studies^[25-31] in which MAC or conscious sedation used for analgesia for IVF are summarized in Table 1.

General anesthesia

Most of the anesthetic agents being used in GA have been found in the follicular fluid. However, in a few studies, it was observed that it can be a safer option for anesthesiologists. As the uterus becomes more relaxed under GA, it is easier for the clinician to aspirate a large number of ovarian follicles, unlike sedation where a contracted myometrium may interfere with oocyte retrieval. The duration of GA should be kept minimum to avoid detrimental effects of these drugs on oocytes. The various studies^[32-34] in which GA used for analgesia for IVF are summarized in Table 2.

Table 1: MAC, conscious sedation, and IVF outcome

Authors	Outcome	Study design
Wilhelm <i>et al.</i> ^[19]	MAC with remifentanyl resulted in a higher pregnancy rate (30.6%) than GA with alfentanil + propofol for induction and isoflurane + propofol for maintenance (17.9%)	Retrospective analysis in 251 patients
Hadimioglu <i>et al.</i> ^[25]	Studied various combination of sedation regimens (propofol plus fentanyl, propofol plus alfentanil, midazolam plus fentanyl, or midazolam plus alfentanil) for oocyte retrieval and found no significant difference between propofol + fentanyl, midazolam + fentanyl and propofol + fentanyl in the recovery characteristics	Prospective study in 60 patients (15 in each group)
Soussis <i>et al.</i> ^[26]	Investigated the time course of changes in follicular fluid concentrations of midazolam, fentanyl, and alfentanil during ultrasound-guided transvaginal oocyte collection. Midazolam was found to be safe for sedation in oocyte retrieval	Prospective study in 45 patients
Ben-Shlomo <i>et al.</i> ^[27]	GA with fentanyl, propofol, and isoflurane resulted in a similar pregnancy rate in comparison to sedation with midazolam and ketamine for transvaginal oocyte retrieval	Randomized prospective design in 50 patients
Bein and Klapproth ^[28]	IV analgesedation with midazolam and fentanyl for IVF procedures was found comfortable, and a high degree of anterograde amnesia was achieved by all the patients	Randomized controlled trial
Trout <i>et al.</i> ^[29]	Reviewed the principles and practice of the use of conscious sedation (opioids in combination with benzodiazepines) for IVF. They concluded that it is a safe and cost-effective method and well-tolerated by patients and does not require highly specialized equipment	Literature review
Fiebai <i>et al.</i> ^[30]	Evaluated patient's pain experience, acceptance of conscious sedation and correlation of pain during oocyte retrieval for IVF. They found that mean pain score was low, and the duration of the procedure did not significantly influence the pain intensity	Cross-sectional survey
Vlahos <i>et al.</i> ^[16]	Gave an update on anesthesia practices used at that time in the United States and Europe in IVF technology. Conscious sedation is relatively safer and easy to administer in cooperative patients. A combination of propofol, fentanyl, and midazolam is used most commonly	Electronic search of MEDLINE for literature published between 1972 and 2008
Lok <i>et al.</i> ^[31]	Compared patient-controlled sedation using propofol plus alfentanil and physician-administered sedation using diazepam plus pethidine (administered IV 5-10 min prior to the procedure during transvaginal ultrasound-guided oocyte retrieval). They found that although patient-controlled sedation provided less analgesia than physician controlled sedation but it is safe, satisfactory, and accepted by patients	Prospective randomized trial of 106 patients

IVF: *In vitro* fertilization, MAC: Monitored anesthesia care, GA: General anesthesia, IV: Intravenous, N₂O: Nitrous oxide

Table 2: GA and IVF outcome

Authors	Outcome	Study design
Boyers <i>et al.</i> ^[32]	GA (isoflurane or enflurane with 50% N ₂ O and 50% oxygen) for laparoscopic techniques for IVF may adversely affect oocyte quality and less likely to be fertilized if the duration of the procedure was prolonged because of acidification of follicular fluid by intraperitoneal carbon dioxide	Prospective study of 305 consecutive cycles of laparoscopy
Hayes <i>et al.</i> ^[33]	Anesthesia length, CO ₂ pneumoperitoneum, increased prolactin, decreased gonadotropins, ovarian trauma, and time significantly predicted fertilization	Retrospective analysis of 3 1/2 years experience with IVF
Van der Ven <i>et al.</i> ^[34]	Investigated the effect of GA (thiopentone and alfentanil) on the embryo transfer. The overall pregnancy rate was 36% (n=86), compared to 21% in a group of matched controls without anesthesia. The results of this study indicated no obviously adverse effect of the anesthesia on the induction of pregnancy	Prospective trial on 131 patients

GA: General anesthesia, IVF: *In vitro* fertilization

Paracervical and preovarian block

In PCB, a local anesthetic is injected into 2-6 sites at a depth of 3-7 mm alongside the vaginal portion of the cervix in the vaginal fornices. In comparatively newer technique, preovarian block (POB), the local anesthetic is infiltrated in the vaginal wall under ultrasound guidance between the vaginal wall and peritoneal surface near the ovary.^[35] The various studies^[36-40] in which paracervical or POB used for analgesia for IVF are summarized in Table 3.

Spinal anesthesia

Spinal anesthesia is also an efficient method for oocyte retrieval. The various studies^[41-47] in which spinal anesthesia used for IVF

are summarized in Table 4.

Epidural anesthesia

Epidural anesthesia is another mode of analgesia for IVF, and it can be a viable option in some conditions. The various studies^[48,49] in which epidural anesthesia used for IVF are summarized in Table 5.

Total intravenous anesthesia

Raftery and Sherry^[50] in their study on 80 women found that TIVA with propofol and alfentanil is superior to inhalational anesthesia with N₂O and enflurane in view of less nausea and vomiting (64% in inhalational group and 39% in TIVA

Table 3: Paracervical, POB, and IVF outcome

Authors	Outcome	Study design
Corson <i>et al.</i> ^[36]	PCB with bupivacaine for pain relief during oocyte aspiration compared with placebo injection was associated with lower pain scores for oocyte retrieval process	Prospective, randomized, double-blinded, placebo-controlled trial on 101 patients
Ng <i>et al.</i> ^[37]	Various conscious sedation regimens using midazolam, diazepam, alfentanil used along with PCB to enhance the analgesia. They observed that patients who received only a PCB during the egg collection experienced 2.5 times higher levels of vaginal and abdominal pain as compared to those who received both PCB and conscious sedation	Prospective, randomized, double-blind trial on 150 patients
Ng <i>et al.</i> ^[38]	Compared the effectiveness of three different doses of lignocaine (50, 100, and 150 mg) used in PCB during transvaginal ultrasound-guided oocyte retrieval. Vaginal and abdominal pain levels during oocyte retrieval and 4 h after were not significantly different among the three groups. They recommended 50 mg of lignocaine for PCB because of the lack of improvement in pain relief on higher doses and potential dose-related risks	Randomized double-blind study on 153 patients
Christiaens <i>et al.</i> ^[39]	Found no differences between the fertilization rates when compared propofol and PCB during oocytes collection (13.4 vs. 18.6%; $P=0.10$)	Prospective, case-controlled study on 202 patients
Tummon <i>et al.</i> ^[40]	Pain intensity and the total pain experience were greater with lidocaine vaginal gel compared with lidocaine PCB during oocyte retrieval	Randomized trial on 150 patients
Cerne <i>et al.</i> ^[35]	No differences were found in degree of anxiety, premedication, dose of alfentanil, fertilization rate, number of good-quality embryos or clinical pregnancy rate when POB technique compared with PCB	Prospective, randomized, multicentre study of 183 patients, randomized to POB ($n=96$) or PCB ($n=87$) group

IVF: In vitro fertilization, PCB: Paracervical block, POB: Preovarian block

Table 4: Spinal anesthesia and IVF outcome

Authors	Outcome	Study design
Martin <i>et al.</i> ^[41]	Demonstrated that when low dose fentanyl (10 µg) is added to hyperbaric 1.5% lidocaine (45 mg) in spinal anesthesia for egg retrieval, patients were more comfortable during the procedure compared with those who received lidocaine alone	Randomized controlled trial on 78 patients
Tsen <i>et al.</i> ^[42]	Compared intrathecal hyperbaric bupivacaine 3.75 mg (0.5 mL of 0.75%) with fentanyl 25 µg versus hyperbaric lidocaine 30 mg (2.0 mL of 1.5%) with fentanyl 25 µg for oocyte retrieval and did not find any combination superior to other	Prospective, randomized, double-blinded study on 40 patients
Endler <i>et al.</i> ^[43]	By using subarachnoid block in 4 patients, they obtained ova in 3 patients, and two of them became pregnant and delivered healthy full-term infants. They inferred that regional anesthesia in selected cases is a useful alternative method of providing anesthesia for the retrieval of oocytes when GA is not indicated	Case series in 4 patients
Viscomi <i>et al.</i> ^[44]	Compared spinal anesthesia (hyperbaric 5% lidocaine, 50-80 mg) versus IV sedation (alfentanil plus midazolam) for transvaginal oocyte retrieval. Both groups had similar reproductive outcomes. The IV sedation group required a significantly longer period until recovery room discharge criteria were met ($P=0.03$), and were more likely to have postoperative emetic episodes (46% vs. 6% in the spinal anesthesia group: $P<0.01$)	Pilot study-retrospective review during a 2-year interval ($n=95$, spinal anesthesia - 51, IV sedation group - 44)
Manica <i>et al.</i> ^[45]	They observed that the use of 1.5% hyperbaric lidocaine with 10 µg fentanyl in spinal anesthesia for transvaginal oocyte retrieval provided a significantly shorter recovery time when compared to 5% hyperbaric lidocaine. The group receiving 1.5% lidocaine had significantly shorter times to ambulation (141±21 min vs. 162±29 min; $P<0.05$), voiding (147±21 min vs. 174±28 min; $P<0.05$), full motor recovery (86±21 min vs. 111±22 min; $P<0.0001$), and discharge (170±38 min vs. 201±41 min; $P<0.05$)	Randomized controlled trial of 56 patients
Aghaamoo <i>et al.</i> ^[46]	Recommended to use spinal anesthesia instead of GA for oocyte retrieval to achieve successful IVF outcome as increased chance of pregnancy (OR=2.07; 95% CI: 1.02,4.20; $P=0.043$) with spinal anesthesia	Cohort study
Azmude <i>et al.</i> ^[47]	Demonstrated that spinal anesthesia (27%) increased the chance of fertilization success in comparison to GA (15%)	Randomized clinical trial on 200 patients

IVF: In vitro fertilization, OR: Odds ratio, CI: Confidence interval, GA: General anesthesia, IV: Intravenous

group), less requirement for anti-emetic medication (62% in inhalational group and 32% TIVA group), and a lower probability of unplanned admission to hospital (21% in inhalational group and 5% in TIVA group) after day-care IVF procedures.

Patient controlled analgesia (PCA)

It is an alternative technique of analgesia with higher levels of patient satisfaction by allowing women to control over their drug administration. Bhattacharya *et al.*^[51] in a prospective randomized study compared the effect of fentanyl administered either through a PCA pump (10 µg fentanyl bolus with 1 min lockout interval) or by a physician. The mean pain score in the PCA group was 38.5 (19.8) while in the other group, it

Table 5: Epidural anesthesia and IVF outcome

Authors	Outcome	Study design
Lehtinen <i>et al.</i> ^[48]	Studied the effects of epidural analgesia and GA (fentanyl, thiopentone, and N ₂ O) on stress hormone release during laparoscopy for IVF. They observed that neither mode of anesthesia prevented the stress response to laparoscopy and mean plasma level of progesterone was significantly greater in the epidural than in the GA group, suggesting that the mode of anesthesia may have an effect on the luteal phase	Prospective comparative study in 24 women
Botta <i>et al.</i> ^[49]	Found epidural anesthesia as an effective method for transvaginal oocyte retrieval but it did not improve the treatment outcome (fertilization, cleavage, and pregnancy rates were 67.2%, 92%, and 20%, respectively) as compared to an IV sedation with mask-assisted ventilation using propofol and N ₂ O (fertilization, cleavage, and pregnancy rates 69.3%, 93%, and 19.6%, respectively)	Randomized controlled trial on 148 patients (epidural anesthesia-44 and IV sedation-104)

IVF: *In vitro* fertilization, GA: General anesthesia, IV: Intravenous

Table 6: Local anesthetic agents and IVF outcome

Authors	Outcome	Study design
Schnell <i>et al.</i> ^[55]	Demonstrated that lidocaine and 2-chloroprocaine adversely affected both fertilization and embryo development at concentrations of 1.0 and 0.1 mg/mL, respectively. In contrast, bupivacaine produced adverse effects only at the high concentration (100 mg/mL)	The effect of local anesthetics on fertilization and development in women undergoing IVF was examined in a mouse IVF system
Tsen <i>et al.</i> ^[42]	Bupivacaine compared favorably to lidocaine in all aspect except taking approximately 30 min longer to micturition and discharge	
Wikland <i>et al.</i> ^[56]	Reported that the incidence of oocyte fertilization and clinical pregnancy was not reduced among women who received a modified PCB with lidocaine for transvaginal oocyte retrieval	Prospective comparative study in 92 women

IVF: *In vitro* fertilization, PCB: Paracervical block

was 46.1 (21.3) ($P = 0.1$). In the PCA group, 64% of women felt very satisfied with their analgesia as compared with 57% in the non-PCA group ($P = 0.6$). They concluded that although intraoperative PCA with fentanyl is an effective alternative to physician-administered techniques in terms of patient comfort and satisfaction.

Acupuncture

It is a conventional therapy which activates the endogenous opioid system by increasing beta-endorphin levels.^[52] It has the additional benefit of providing antidepressant, anxiolytic, and sympathoinhibitory actions. It has been used along with various conscious sedation regimens and paracervical block to enhance analgesia during IVF procedures. Humaidan and Stener-Victorin^[53] in a prospective randomized study in 200 women investigated the role of electroacupuncture as an alternative to the conventional analgesic method (benzodiazepine premedication and alfentanil 0.25 mg boluses). They found that the procedure was well-tolerated in both the groups, however, higher pain scores were observed in electroacupuncture group. Gejervall *et al.* in their randomized study on 160 females found that electroacupuncture cannot be generally recommended as a pain relieving method of oocyte aspiration but might be an alternative for women desiring a nonpharmacological method. In a similar study, Stener-Victorin *et al.*^[54] concluded that analgesic effects produced by electroacupuncture are as good as those produced by conventional analgesics, and the use of opioid analgesics with electroacupuncture is lower than when conventional analgesics alone are used.

Anesthetic agents and *in vitro* fertilization

Local anesthetic agents

The various local anesthetic drugs and their effects^[54,55] on IVF outcomes are summarized in Table 6.

Opioids

Various opioids (fentanyl, alfentanil, remifentanil, and pentazocine) have been used for analgesia for IVF procedures. Their effects^[56-66] on IVF outcomes are summarized in Table 7.

Benzodiazepine

Midazolam is the most commonly used benzodiazepine for IVF procedures. Although a minimal amount of this benzodiazepine is found in the follicular fluid, no deleterious effects have been demonstrated. The benzodiazepines and their effects^[67,68] on IVF outcomes are summarized in Table 8.

Ketamine

The effect of ketamine^[69] on IVF outcomes is summarized in Table 9.

Propofol and thiopental

Propofol and thiopentone are being used extensively in IVF, and their effects on the fertilization, embryo cleavage, and pregnancy rates have been investigated in various studies^[70-77] [Table 10]. Propofol is suitable for day care IVF procedures with added advantages of the antiemetic property along with faster recovery.

Table 7: Opioids and IVF outcome

Authors	Outcome	Study design
Bruce <i>et al.</i> ^[57]	Authors found that fentanyl did not affect fertilization and subsequent cell division when present in concentrations calculated to approximate or exceed those to which human oocytes exposed during clinical anesthesia	Sea urchin eggs were used to observe the effects of fentanyl on IVF and early development as a model of human IVF
Shapira <i>et al.</i> ^[58]	Compared alfentanil (0.025 mg/kg) with fentanyl (0.0025 mg/kg) for anesthesia for IVF and observed shorter induction time for alfentanil (1.3±0.7 min) than for fentanyl (3.4±2.2) and less drowsy patients who received alfentanil	Prospective double-blind study on 36 women (19 in alfentanil group and 17 in fentanyl group)
Shapira <i>et al.</i> ^[59]	Found low accumulation of alfentanil in the follicular fluid as alfentanil concentrations in the follicular fluid was about ten-fold smaller than the serum alfentanil concentrations at the same time points	Observational study in 14 patients
Wilhelm <i>et al.</i> ^[21]	Studied the effect of remifentanyl (0.25 µg/kg/min) infusion on transvaginal puncture for oocyte retrieval and concluded that sole infusion of remifentanyl was a suitable and satisfying single-agent for oocyte retrieval	Prospective trial on 50 patients
Casati <i>et al.</i> ^[60]	Compared propofol/fentanyl with midazolam/remifentanyl based anesthesia on healthy women undergoing ultrasound-guided oocyte retrieval for IVF procedures. The time to achieve an Aldrete's score of 10 was shorter in the midazolam/remifentanyl patients group (2±2 min) than in those who received propofol/fentanyl (4±2 min). Authors concluded that both regimens are effective and safe	Randomized controlled trial in 60 patients
Hammadeh <i>et al.</i> ^[61]	Compared the effects of GA (remifentanyl with either propofol or isoflurane and sedation (midazolam, diazepam or propofol) used for oocyte retrieval. They found no significant differences in cleavage and pregnancy rates between these two groups	Prospective comparative study in 202 women (96 in sedation group and 106 in GA group)
Gunaydin <i>et al.</i> ^[62]	Compared plasma remifentanyl concentrations and pulmonary function tests in patients receiving remifentanyl infusion versus remifentanyl infusion with PCB during transvaginal ultrasound-guided oocyte retrieval. Both anesthesia regimens provided satisfactory analgesia without affecting FEV ₁ and FVC, but significantly higher plasma remifentanyl concentrations were calculated when only remifentanyl infusion was used as an anesthetic technique	Randomized controlled trial on 40 patients. 20 patients in both the groups
Matsota <i>et al.</i> ^[63]	No significant difference found when analgesia with remifentanyl compared with anesthesia with propofol and alfentanil during ultrasound-guided transvaginal oocyte retrieval	Randomized trial on 58 patients
Milanini <i>et al.</i> ^[64]	Compared local anesthesia with continuous IV administration of remifentanyl for oocyte retrieval. They found that remifentanyl did not interfere in the quality of oocytes retrieved, and it made easier the pick-up of oocytes because women had no pain during the procedure	Retrospective study on 548 women
Coskun <i>et al.</i> ^[65]	Observed similar pain-free conscious sedation conditions in three different target-controlled remifentanyl infusion rates groups (1.5, 2, and 2.5 ng/mL) during target-controlled propofol infusion (1.5 µg/mL) for oocytes retrieval. The 1.5 or 2 ng/mL group proved superior at providing early recovery compared to 2.5 ng/mL	Prospective comparative study on 69 patients
Jarhazadeh <i>et al.</i> ^[66]	Observed that in women undergoing transvaginal ultrasound-guided oocyte retrieval procedures, the likelihood of a successful pregnancy was higher with a remifentanyl-based anesthesia than with a fentanyl-based anesthesia. The recovery from anesthesia was significantly better in the remifentanyl group versus fentanyl group	Randomized, double-blind clinical trial on 145 patients
Liang <i>et al.</i> ^[67]	Subclinical doses of pentazocine (0.4 mg/kg pentazocine with 1.5 mg/kg propofol) showed greater intraoperative consciousness but with more stable respiration in comparison to control group (0.5 mg/kg pentazocine with 1.5 mg/kg propofol) for oocyte retrieval	Randomized controlled trial on 81 women

IVF: *In vitro* fertilization, GA: General anesthesia, PCB: Paracervical block, FEV₁: Forced expiratory volume in 1 s, FVC: Forced vital capacity, IV: Intravenous

Table 8: Benzodiazepines and IVF outcome

Authors	Outcome	Study design
Swanson and Leavitt ^[68]	Midazolam administered systemically in preovulatory mice did not impair fertilization or embryo development <i>in vivo</i> or <i>in vitro</i> , even when given in doses up to 500 times those used clinically	Observational study on mouse preimplantation embryo
Casati <i>et al.</i> ^[69]	When used in small bolus or infusion doses for anxiolysis and sedation for IVF procedures in humans, midazolam has not been detected in follicular fluid and does not appear to be teratogenic	Randomized controlled trial in 60 patients

IVF: *In vitro* fertilization

Etomidate

Heytens *et al.*^[79] in a prospective comparative study in 18 patients found that etomidate could also interfere with the endocrine function of the ovary by observing a sharp decrease in the

plasma concentration of 17 beta-oestradiol, progesterone, 17-hydroxyprogesterone -progesterone, and testosterone within 10 min after induction of anesthesia with etomidate (0.25 mg/kg) followed by a gradual return to the baseline levels thereafter.

Table 9: Ketamine and IVF outcome

Authors	Outcome	Study design
Ben-Shlomo <i>et al.</i> ^[27]	Authors reported ketamine 0.75 mg/kg with midazolam 0.06 mg/kg as an acceptable alternative to GA with isoflurane	Randomized prospective study in 50 patients
Sterzik <i>et al.</i> ^[70]	Authors observed increased prolactin and beta-endorphin plasma levels associated with ketamine and GA. They suggested to avoid GA in favor of ketamine for IVF and embryo transfer procedures	Randomized 54 patients into 3 groups (1) ketamine as an induction agent and analgesic ($n=20$); (2) anesthesia using thiopentone for induction and enflurane for maintenance ($n=18$) (3) no anesthesia ($n=16$)

GA: General anesthesia, IVF: *In vitro* fertilization

Table 10: Propofol and thiopental

Authors	Outcome	Study design
Endler <i>et al.</i> ^[71]	Both thiopental and thiamylal (5 mg/kg) detected in follicular fluid as early as 11 min after their administration for induction of GA in patients undergoing laparoscopic IVF procedures	Observation study in 24 patients thiopental ($n=15$) and thiamylal ($n=9$)
Pierce <i>et al.</i> ^[72]	No significant difference was observed in pregnancy rates between thiopental (24.6%) and propofol (25.8%) groups, respectively	Retrospective review in 230 women
Ben-Shlomo <i>et al.</i> ^[73]	No significant difference found on IVF outcome, cleavage and embryo with exposure to increasing concentrations of propofol	Cohort study on 130 women
Vincent <i>et al.</i> ^[74]	Observed that propofol/ N_2O anesthesia was associated with lower pregnancy rates compared with isoflurane/ N_2O anesthesia (54% vs. 29%, $P=0.014$) in IVF	Randomized clinical trial on 112 patients
De Amici <i>et al.</i> ^[75]	Described continuous IV infusion of propofol in patients undergoing oocyte retrieval during IVF. Authors concluded that it could be carried out in day care units with complete safety and good acceptability from the patients	Description of a method
Coetsier <i>et al.</i> ^[76]	Investigated the concentrations of propofol in follicular fluid at fixed intervals during oocyte retrieval. They did not find any unfavorable effect of propofol on IVF, but suggested that this procedure should be kept as short as possible in order to limit accumulation of anesthetic drugs in follicular fluid	Observational study in 9 patients
Huang <i>et al.</i> ^[77]	No significant differences found between propofol and thiopentone groups for induction of GA during oocyte retrieval on fertilization rate (68.9% for propofol group and 66.7% for thiopentone) ($P=0.614$), cleavage rate, pregnancy rate, implantation rate, and abortion rate	Retrospective study of 92 cases (72 cases in propofol group and 20 cases in thiopentone group)
Handa-Tsutsui and Kodaka ^[78]	By using target-controlled infusion authors determined the target concentration of propofol required to prevent movement in 50% (Cp50) and 95% (Cp95) of women during oocyte retrieval and investigated whether supplemental N_2O modified these values. Authors found Cp50 of propofol, 4.1 $\mu\text{g}/\text{mL}$ in the control group and 3.3 $\mu\text{g}/\text{mL}$ in the N_2O group (reduced by a factor of 1.24)	Randomized controlled trial on 47 women (23 in control group; O_2 -air mixture and 24 in O_2 - N_2O mixture group)

GA: General anesthesia, IVF: *In vitro* fertilization, IV: Intravenous

Nitrous oxide

Gonen *et al.*^[80] in their retrospective analysis of three groups sedation combined with local anesthesia, epidural block, and GA with N_2O found that N_2O had a deleterious effect on IVF outcome. Significantly lower clinical pregnancy rates were found in N_2O group (14.5%) compared with epidural group (23.7%; $P = 0.018$) or sedation group (25.8%; $P = 0.0074$). N_2O deactivates methionine synthetase thereby reducing the amount of thymidine available for DNA synthesis in dividing cells. However, this effect is minimal as the inactivation of methionine proceeds slowly in the human liver. Moreover, the low solubility of N_2O exposes the oocytes to this gas for a short duration. In contrary to this, Hadimioglu *et al.*^[25] demonstrated that N_2O increase the success rate of IVF by lowering the concentration of other potentially toxic and less diffusible anesthetic drugs. Thus, the effect of N_2O on IVF outcome still remains questionable.

Volatile halogenated agents

Most of the studies have demonstrated the deleterious effect of halogenated fluorocarbons on IVF outcomes. Matt *et al.*^[81] observed insignificant effect of N_2O and isoflurane anesthesia on human IVF pregnancy rate. The effects of various volatile agents^[81-87] on IVF outcome are summarized in Table 11.

Postoperative nausea and vomiting and antiemetic agents

Postoperative nausea and vomiting (PONV) is a common problem after IVF procedures under anesthesia,^[88,89] and its frequency is related to peak plasma level of estradiol and previous history of PONV [Table 12]. Higher incidence of PONV was found following inhalational anesthesia for IVF procedures as compared to TIVA.

Bromocriptine

Sopelak *et al.*^[91] in their study on 32 patients observed that bromocriptine, a potent dopamine agonist, given before anesthesia can suppress transient, anesthesia-induced

Table 11: Volatile halogenated agents

Authors	Outcome	Study design
Chetkowski and Nass ^[82]	Isflurane adversely affects embryo development <i>in vitro</i>	Observational study on mouse embryo
Warren <i>et al.</i> ^[83]	Reported that two-cell mouse embryos exposed to 3% isoflurane for 1 h were less likely to develop to the blastocyst stage. As with their earlier study of embryos exposed to N ₂ O, these researchers noted that the timing of anesthetic administration was critical. Developmental outcome was impaired only when isoflurane was given within 4 h of the predicted onset of cleavage	Observational study on mouse embryo development
Critchlow <i>et al.</i> ^[84]	Reported lower pregnancy and delivery rates among women who received halothane for IVF procedures than in women who received enflurane	Retrospective survey of 47 patients over a 18-month period
Eger <i>et al.</i> ^[85]	Metabolic byproduct of sevoflurane, compound A associated with genotoxic ovarian cell effects, although reproductive outcomes had not been assessed in their study	Observational study on Chinese hamster oocytes
Fishel <i>et al.</i> ^[86]	Halothane significantly reduced the incidence of implantation compared to enflurane 34% and 17%, respectively ($P=0.005$)	Observational study on 356 replacements
Naito <i>et al.</i> ^[87]	Higher plasma prolactin levels and lower plasma progesterone levels were observed in the neurolept anesthesia (with droperidol and fentanyl) group than in the halothane group during and after transvaginal ultrasound-guided oocyte pick-up	Prospective comparative study in 12 patients (7 in halothane anesthesia group and 5 in neurolept anesthesia group)
Pirola <i>et al.</i> ^[88]	Compared 4 analgesic methods (EMLA cream, propofol, thiopental sodium, sevoflurane) for IVF oocyte retrieval. Fertilization rate in the EMLA and sevoflurane groups were similar but significantly higher than the propofol and thiopental sodium groups ($P<0.001$). Authors concluded that a local anesthetic cream could be proposed as an acceptable alternative option for anesthesia during transvaginal oocyte retrieval	Retrospective comparative study on 100 patients

IVF: *In vitro* fertilization**Table 12: Antiemetic agents, PONV and IVF outcome**

Authors	Outcome	Study design
Kaupila <i>et al.</i> ^[89]	Authors found that metoclopramide induced hyperprolactinemia with subsequent impairment of ovarian follicle maturation and corpus luteum function. They concluded that when these agents are given as a single dose immediately prior to oocyte retrieval, it is unlikely that the mature oocyte will be affected; however, if they are given on a routine basis after retrieval, the uterine receptivity to the embryo could be affected	Observational study
Coburn <i>et al.</i> ^[90]	Documented PONV in 504 patients received GA for oocyte retrieval for IVF. Authors concluded that the likelihood of vomiting was related to peak plasma oestradiol level and the patient's expectation based on previous experience of anesthesia	Retrospective data analysis of 507 IVF procedures

IVF: *In vitro* fertilization, PONV: Postoperative nausea and vomiting, GA: General anesthesia

hyperprolactinemia, and had have a positive influence on embryonic development.

Nonsteroidal anti-inflammatory drugs

Mialon *et al.*^[92] in a retrospective study compared two analgesic protocols: Paracetamol/alprazolam and nefopam/ketoprofen on IVF outcomes. They found that both groups had similar IVF outcomes and nefopam/ketoprofen protocol enhanced patient comfort without jeopardizing the IVF success rates.

CONCLUSION

The role of the anesthetist in IVF is to provide adequate comfort and pain relief to the patients during oocytes retrieval and embryo transfer procedures. The modality of the providing the same should depend on the patient cooperation. If the patient is comfortable, conscious sedation is a good option. However, in some cases, regional or GA

may be requested. Different studies have explored the effect of anesthesia on IVF outcome but have yielded contradictory findings. These differences may be attributed in relation to differences in the study design and randomization, the anesthetic drugs used, or the anesthetic technique performed. Always pay attention to the comorbidities including those contributing to infertility and the drugs that the patient is taking. Furthermore, the anesthesia should be used for the shortest duration required.

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