

Assisted Reproductive Technology and Anesthetic considerations: Review Of Literature

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Abstract

In-Vitro-fertilization (IVF) is increasingly being practiced in different parts of the world. Anesthesiologists are faced with peculiar challenge to follow an anaesthetic technique that allays patient anxiety with adequate pain relief and yet avoiding any deleterious effect on outcome of successful pregnancy.

Variety of anaesthetic techniques and analgesic methods has been used but no definite conclusion has yet been arrived regarding the technique of choice for IVF. No method could be considered as superior to other technique if basic concepts pertaining to IVF are taken care. Conscious sedation is suitable for cooperative females. In addition to conscious sedation and analgesia, many methods of pain relief during oocyte recovery are currently in use. In case general anaesthesia is required, the anaesthetic drugs should be used cautiously and efforts should be made to reduce the anaesthetic duration. The preferred modality of peri-operative care should be individualized as per the requirement of the patient.

INTRODUCTION

The first successful live birth following in-vitro fertilization (IVF) of a human oocyte was performed in 1978 by Steptoe and Edwards with the birth of Lousie Brown, the first test tube baby. Assisted Reproductive Technology (ART) has gradually evolved into more sophisticated with advancement and better outcome. Similarly the related anaesthetic techniques as well. The anesthesiologist may be involved in many aspects of the patient's treatment, which may be complex and needs cautious peri-operative management. IVF is a four stage procedure – ovarian stimulation and monitoring, oocyte retrieval, fertilization and embryo transfer. Egg retrieval can be accomplished laparoscopically or ultrasound guided vaginal retrieval.

NEED OF ANESTHESIOLOGIST

Majority of the patients are young and healthy but exhibit stress, anxiety and other psychological disorders associated with infertility. It is particularly important for the anesthesiologist to understand the patient's anxieties and take suitable measures to allay it. The serum hyperprolactinaemic response to stress is well established¹. 50-fold transient increase in serum prolactin levels during oocyte retrieval for in-vitro fertilization has been reported under general anaesthesia which may influence the outcome of IVF^{2,3,4,5}. The need of repeated attempts of IVF before success is

achieved, also mandates taking care of psychological stress and alleviating it. The IVF procedures are also associated with pain and hence the need of minimization of pain is a major consideration⁶. The cooperation of patient is required during IVF procedure like oocyte retrieval, which some time mandates the need of anaesthesia even.

ANAESTHETIC CONSIDERATIONS

For ART procedures, the factors to be taken under considerations includes the technique of anaesthesia, pneumoperitoneum (if laparoscopy required), and the effects of anaesthetic agents on fertilization and cell cleavage. The length of exposure to drugs is also important. Now a days, the ART procedures are being accomplished as 'Day care' cases and the basic principles of 'Ambulatory anaesthesia' needs to be followed. Laparoscopic oocyte retrieval has now largely been superseded by ultrasound-guided transvaginal oocyte retrieval⁵.

EFFECT OF ANAESTHETIC AGENTS ON REPRODUCTIVE TECHNIQUES

Controversy exists regarding the effects of anesthetic drugs administered during transvaginal puncture procedures for oocyte retrieval on conception rates⁷. Anesthetics have been detected in follicular fluid, and studies suggest that these drugs may adversely affect oocyte fertilization and embryonic development. It has also been confirmed that the

use of general anaesthesia with nitrous oxide for oocyte retrieval has an adverse outcome on the outcome of IVF; the deleterious effect manifests itself only after embryo transfer and leads to lower pregnancy and delivery rates^{8,9}. Exposure to pneumoperitoneum with carbon-di-oxide adversely affects oocyte quality and in combination with exposure to general anaesthesia with nitrous oxide appear to affect fertilization and cleavage in vitro⁷. However, Rosen et al failed to demonstrate an adverse effect of nitrous oxide on fertilization or pregnancy rates when administered during an isoflurane-based general anesthetic technique¹⁰. Anesthetic drugs have been detected in follicular fluid, and a longer period of exposure in the general anesthesia group may have enhanced the deleterious effects of these drugs on the oocyte and/or follicular structures, thereby interfering with the reproductive process^{11,12,13,14}. Halogenated agents have been associated with reduced reproductive success in clinical practice and must therefore be used with caution^{7,15}. Opioids, and especially fentanyl and remifentanyl, do not seem to affect reproductive success.

Exposure to high concentrations of different local anesthetics adversely affects fertilization and embryonic development¹⁶. However, given that much lower concentrations are achieved clinically and that oocytes are washed after retrieval, the clinical effects of using local anesthetics should be limited and probably no adverse effects should occur.

PAIN IN IVF

Oocyte retrieval is a fundamental step but reported to be the most painful component of the IVF procedure^{17,18,19}. Although less invasive than the laparoscopic approach, transvaginal oocyte retrieval still remains a painful procedure^{20,21}. The pain experienced during oocyte aspiration is caused by the passage of the needle through the vaginal wall and by mechanical stimulation of the ovary^{6,22}. The pain is often described as similar to intensive menstrual pain and is intermittent rather than continuous. Factors that may influence the pain are the number of follicles, duration of the oocyte retrieval procedure, the position and mobility of the ovaries²². Multiple-follicle aspiration would entail a lengthier procedure, which could affect pain scores when compared with single-follicle aspiration²³. A good analgesic method for oocyte retrieval has to give satisfactory pain relief with rapid onset, rapid recovery, ease of administration and monitoring^{17,18,19}. In addition, the analgesic method must have no toxic effects on the oocytes and embryos since many agents have been detected in the follicular fluid shortly

after administration^{24,25,26,27}.

For alleviating pain of IVF, opioids and benzodiazepines has been used, however, many of these agents have been detected in the follicular fluid, albeit clear evidence to indicate negative effects on oocytes, oocyte differentiation, implantation or pregnancy rate is sparse. More and more patients, however, are requesting sedation or anaesthesia for ultrasound-guided oocyte retrieval. It is also important to use anaesthetic agents that are safe, has no toxic effects on the oocytes and ensures the highest fertilization and pregnancy rates^{17,28}.

IVF ANAESTHESIA TECHNIQUES

Transvaginal ultrasound-guided oocyte retrieval as a part of in vitro fertilization is the most common method of oocyte retrieval and is a relatively short (20±30 minutes) outpatient procedure^{19,22,28}. As such, it requires an anesthetic technique that works quickly and effectively during the procedure but also allows for a rapid recovery with minimal side effects.

Traditional analgesic methods used for transvaginal oocyte retrieval include local injection as a paracervical block, conscious sedation using various pharmacological agents, epidural block, subarachnoid block, general anaesthesia, or in some cases no analgesic at all^{6,23,21,29,30,31,32,33,34,35,36}. The principle of a balanced multimodal approach to analgesia has been shown to be effective at treating pain in other clinical settings such as cancer²³. The end point of in vitro fertilization procedures is ultimately the rate of successful pregnancies. Viscomi et al found no difference in fertilization and pregnancy rates between intravenous sedation and spinal anesthesia³⁷. Rosenblatt et al noted that the addition of propofol to intravenous sedation for egg retrieval did not affect pregnancy and implantation rates³⁸. Gonen et al did find that general anesthesia with a number of drugs was associated with decreased pregnancy rates when compared with epidural anesthesia³⁹.

In a systemic review by Stener-Victorin for methods of conscious sedation during assisted reproduction techniques, concluded that no single technique may be regarded as superior to other for pain relief during oocyte retrieval⁶. Similarly, in an another Cochrane review by Kwan et al and found, on analysis of studies regarding conscious sedation and other alternate techniques of pain relief, that no single method or delivery system appeared superior for pregnancy rates and pain relief²³. Various methods for analgesia reviewed were sedation with midazolam, ketamine, fentanyl,

alfentanil or electro acupuncture along with paracervical block, intramuscular pethidine and/or piroxicam and general anaesthesia with intravenous fentanyl and propofol. It was concluded that there is insufficient evidence to determine the best method of pain relief for oocyte retrieval .

Monitored anesthesia care or intravenous sedation with fentanyl and midazolam was used for egg retrieval, but patient discomfort and motion during the procedure led to the use of other anesthetic techniques ²⁸ . Spinal anesthesia has been used because it provides excellent surgical anesthesia with minimal use of intravenous medication. An alternate technique is intravenous general anesthesia with fentanyl, midazolam, and propofol.

General anaesthesia will abolish the issue of pain during oocyte retrieval but is likely to have resource implications. In choosing appropriate regimens for sedation/analgesia for oocyte retrieval, a balance may need to be struck between safety and efficacy. The ideal regimen would reduce pain to a tolerable level in all patients without the risk of adverse respiratory or cardiovascular events ²³ . Conscious sedation allows patient co-operation to be maintained and the procedure to be conveniently performed in the outpatient setting. This remains the most commonly used method of providing analgesia and anaesthesia during transvaginal oocyte retrieval and is used in 84% of IVF clinics in the UK and 95% of IVF centers in the USA. By comparison, 16% of UK clinics and about 50% of clinics in Germany use general anaesthesia for IVF procedures ²³ .

GENERAL ANAESTHESIA

Wilhelm et al compared the outcome of assisted reproductive technology procedures in 251 women who undergo monitored anaesthesia care with remifentanil versus general anesthesia (alfentanil, propofol, isoflurane, nitrous oxide) ⁷ . They concluded that the pregnancy rates in women undergoing transvaginal oocyte retrieval for assisted reproductive technologies were significantly higher with a remifentanil-based MAC technique than with a balanced general anesthetic technique involving nitrous oxide.

REGIONAL / LOCAL ANAESTHESIA

In a study by Zaccabri et al vaginal application of EMLA was compared with paracervical block for Oocyte Retrieval. Pain was evaluated by visual analog score (VAS) and the outcome was that no one protocol satisfied the patients; authors suggested improvement of premedication strategies. Intervention such as paracervical block when added to the

opiate conferred further benefit ²³ . Paracervical block induces good analgesia, which is enhanced further by intravenous sedation ⁶ . In study of the intraoperative pain scores associated with intravenous fentanyl plus paracervical block versus electro-acupuncture plus paracervical block favored intravenous fentanyl for IVF ²³ . Paracervical block with bupivacaine was superior to paracervical block with saline or no treatment and oral diazepam, and intravenous alfentanil in combination with paracervical block was superior to electro-acupuncture in combination with paracervical block ^{6,24} . Regarding abdominal pain 60–120 min after oocyte retrieval, electro-acupuncture was superior to intravenous alfentanil, in combination with both paracervical block. Randomized, controlled trials suggest that pain relief is superior when a paracervical block is used in addition to sedation, as compared with sedation alone ^{17,2} . It has also been shown that patients who received only paracervical block during oocyte collection experienced 2.5 times higher levels of vaginal and abdominal pain than those who received both paracervical block and conscious sedation ¹⁷ . A new technique, pre-ovarian block (POB), has been introduced by one of the authors of this study (I.Ek) ¹⁷ . The local anaesthetic is infiltrated under ultrasound guidance in the vaginal wall and between the vaginal wall and the peritoneal surface near the ovary. The follicle aspiration needle is then inserted in exactly the same location as the deposited lidocaine. Cerne et al studied pre-ovarian block versus paracervical block for oocyte retrieval in prospective, randomized, multicentre study including 183 patients ¹⁷ . All participants in both the groups received alfentanil 0.25 – 0.5 mg intravenously prior to procedure. Rescue analgesia was provided with bolus alfentanil 0.25 mg. All patients received rectal paracetamol 1 g preoperatively. Anxiolysis was given by oral flunitrazepam 0.5 mg or 2.5 mg of midazolam. They concluded that both techniques provided comparable pain relief and both pre-ovarian and paracervical block in combination with intravenous alfentanil may be considered safe methods with rapid onset, recovery and ease of administration. A paracervical block (PCB), in combination with different sedative pre-medications with or without fast-acting opiates, has been reported to give acceptable pain relief during oocyte aspiration in several studies ²² . Hung et al concluded from his prospective, randomized, double blind and placebo controlled study to assess the efficacy of paracervical block in the pain relief during egg collection in IVF that paracervical block with lignocaine should be used in conjunction with iv sedation / analgesia (50 mg pethidine and 25 mg promethazine given 1

hour prior and 25 mg pethidine and 5 mg diazepam given 5-10 minutes prior to procedure) during egg collection performed through the transvaginal route under ultrasound guidance to reduce the pain of the procedure ⁴⁰ .

A possible risk associated with paracervical block is the potential toxicity of absorbed lidocaine ^{24,41} . In human use, however, there is no evidence of adverse events associated with lidocaine ¹⁷ . No adverse effects on fertilization, cleavage or pregnancy rates were shown using paracervical block ²⁴ . Paracervical block with different doses of lidocaine has been studied, and no differences were found in pain levels during oocyte retrieval when 50, 100 or 200 mg was used ^{35,36} . Thus, the lowest dose has been recommended.

Lidocaine is a well-documented local anaesthetic often used for paracervical block (PCB) in pregnant women. It thus seems that the concentration of lidocaine found in the follicular fluid after PCB with 50 mg lidocaine does not negatively affect fertilization of the human oocyte or early cleavage of the human embryo ²⁴ .

Intrathecal fentanyl, in combination with local anesthetics (lidocaine), can improve the quality and prolong the duration of intraoperative analgesia ²⁸ . Epidural anaesthesia, the most popular of the obstetric anaesthetic techniques offers no obvious advantages over the IV sedation or the other methods for Oocyte Retrieval nor does it improve the treatment outcome.

PROPOFOL

Propofol has been a promising alternative for Thiopental for short surgical procedures and has been tried for oocyte retrieval. No significant differences exist between the two drugs as regards the fertilization rate, cleavage rate, pregnancy rate, implantation and abortion rate ²⁷ . However propofol should be used with caution, despite its advantages. Propofol has been suspected of damaging oocytes. Concentrations of propofol have been shown to increase in follicular fluid with time, during oocyte retrieval ²⁶ . A study was designed to assess whether exposure to increasing concentrations of propofol has any measurable effect on in-vitro fertilization, cleavage and embryo development. There was an increase in the concentration from the first to the last follicle, but no difference was found in the ratio of mature to immature oocytes. Nor were any differences found in fertilization, cleavage and embryo cell number ²⁷ . It was concluded that the time elapsed between retrieval of the first and last oocyte does not affect oocyte quality. However it is

advisable that the IVF procedure should be kept as short as possible in order to limit the accumulation of the anaesthetic in the follicular fluids.

SEDATION AND MONITORED ANAESTHESIA CARE (MAC)

Concerns regarding the potentially deleterious effects of anesthetic drugs have led to the use of anesthetic techniques that minimize exposure ⁷ . Increasingly, these procedures are performed with sedative and/or analgesic drugs as part of a monitored anesthesia care (MAC) technique. Trout SW strongly advocates conscious sedation (with opioids and benzodiazepines) for IVF ¹⁹ . Several other studies demonstrated higher pregnancy rates in women who underwent oocyte retrieval under MAC with Remifentanyl infusion than with GA. Midazolam/Remifentanyl regimen was evaluated to be as effective and safe as propofol/fentanyl regimen. Several opioids, such as, pethidine, morphine, fentanyl and remifentanyl, have been used as a part of conscious sedation and monitored anaesthesia care and have been effective at reducing perception of pain.

Lok HI et al in his prospective randomized trial comprising 106 patients comparing patient controlled sedation using propofol (10 mg/mL) and alfentanyl (50 mcg/mL) (bolus dose of 1 mL and effective lock out time of 18 sec) and physician administered sedation using diazepam (0.1 mg/kg) and pethidine (0.5 mg/kg) (administered intravenously 5-10 minutes prior to procedure, and additional doses of pethidine 0.5 mg/kg were given when required) during transvaginal ultrasound guided oocyte retrieval ³² . They concluded that though patient controlled sedation provided less analgesia than physician controlled sedation but it is safe, satisfactory and accepted by patients.

The combination of midazolam and ketamine was compared with general anaesthesia with propofol and isoflurane ⁴² . No intraoperative pain was remembered in either group. Hein et al. presented data on two different MAC techniques that suggested that the pregnancy rate was higher when a combination of midazolam, fentanyl, and propofol (vs. fentanyl, ketamine, and methohexital) was used ⁴³ . Propofol was also used in a more recent study at two different dose levels to achieve either general anesthesia or intravenous sedation; and no difference was found in the pregnancy outcome rates ⁷ . In a comparison between propofol-based general anesthesia and paracervical local anesthetic blockade, Christiaens et al found no differences between the fertilization rates or embryo cleavage characteristics ⁴⁴ .

These investigators also reported that the initial implantation rate after propofol anesthesia (13.4%) was similar to the rate in the local anesthetic group (18.6%)⁷. The results of a retrospective chart review also found no evidence that the administration of propofol during aspiration of ovarian follicles had a negative impact on oocyte cumulative embryo scores, implantation, or pregnancy rates⁴⁴. Remifentanyl, which is a rapid and ultra-short acting opioid analgesic, also has been successfully used for ultrasonic- guided oocyte retrieval procedures as part of a MAC technique^{45,46,47}. The present retrospective study compared pregnancy outcome of ART procedures in women exposed to either general anesthesia or MAC with remifentanyl⁷. This retrospective study suggests that in women undergoing transvaginal ultrasound-guided oocyte retrieval procedures, the likelihood of a successful pregnancy is higher with a remifentanyl-based MAC technique than with a “balanced” general anesthetic technique. These findings are supported by a preliminary report by Toon et al suggesting an increased pregnancy rate in women having spinal compared with general anesthesia for oocyte retrieval⁴⁸. Interestingly, use of electro-acupuncture in combination with a paracervical block for oocyte aspiration was judged a good alternative to an opioid-based MAC technique, with an even higher pregnancy rate⁴⁹.

PATIENT CONTROLLED ANALGESIA (PCA)

PCA may facilitate an individualized approach and, by allowing women a degree of control over their drug administration, lead to higher levels of patient satisfaction⁵⁰. The effect of i.v. PCA was evaluated in two studies and was considered to be as effective as physician-controlled techniques^{31,32}. Bhattacharya et al performed the study to evaluate the efficacy of patient controlled analgesia during oocyte recovery. They premedicated their patients with 4 mg midazolam and 25 mcg of fentanyl. Maintenance bolus doses were then administered by the clinician or by the patient herself using patient controlled analgesia pump (10 mcg fentanyl bolus with 1 min lock out). They concluded patient controlled analgesia fentanyl is an effective alternative to physician administered techniques in terms of patient comfort and satisfaction. Despite high satisfaction rates, many women still feel the need for more analgesia during the procedure³¹.

However, since physician controlled sedation demands higher doses of analgesics and many drugs have been found in the follicular fluid shortly after i.v. injection, it is questionable whether this method is optimal in the present

situation⁶. Patients also reported high levels of satisfaction with intravenous opiates administered by a physician or the patient^{31,32}.

ELECTRO-ACUPUNCTURE (EA)

Recently, electro-acupuncture, activates the endogenous opioid system responsible for pain has been reported to decrease pain during oocyte retrieval and have fewer negative side effects^{18,49,51,52}. Acupuncture is a pain-relieving method that activates endogenous pain-inhibiting systems such as the spinal/ segmental gate mechanism and the endogenous opioid systems⁵². Electro-acupressure was compared with alfentanil infusion and was found to be a good alternative for conventional anaesthesia.

Humaidan et al compared the role of electro-acupuncture as an alternative to conventional analgesic method in an prospective randomized study in 200 women⁵³. Both the groups received paracervical block. The conventional analgesic method used was benzodiazepine premedication, alfentanil 0.25 mg boluses. Rescue analgesia was provided with intravenous alfentanil in both the groups. They found significant difference in intraoperative pain. More pain in electro-acupuncture group was attributed probably to administration of premedication in conventional analgesic group. The procedure was well tolerated in both the groups.

Gejervall et al compared the pain relieving effect and postoperative well being between electro-acupuncture and conventional analgesia in a randomized study in 160 females for oocyte retrieval²². Paracervical block was given in both the groups. Conventional analgesia was provided with intravenous alfentanil along with 0.5 mg flunitrazepam and 1 g paracetamol premedication. Rescue analgesia was provided with alfentanil or notrox. They concluded that electro-acupuncture cannot be generally recommended as a pain relieving method at oocyte aspiration but might be an alternative for women desiring a non-pharmacological method. An advantage of electro-acupuncture is less postoperative tiredness and confusion compared with conventional analgesia.

Stener-Victorin et al evaluated the efficacy of electro-acupuncture as peroperative analgesic method during IVF in two different studies^{18,49}. The electro-acupuncture was compared with alfentanil. Both groups received paracervical block as well. The alfentanil group received 0.5 mg alfentanil and 0.25 mg atropine intravenously directly before a paracervical block was placed and oocyte aspiration began. Rescue analgesia was boluses of alfentanil. They

concluded that analgesic effects produced by electro-acupuncture are as good as those produced by conventional analgesics, and the use of opiate analgesics with electro-acupuncture is lower than when conventional analgesics alone are used. But women experience less abdominal pain, less nausea and less stress at 2 h after oocyte aspiration, and also use less opiate analgesics than when conventional analgesics alone are used.

CONCLUSION

A variety of anaesthetic techniques and analgesic methods has been used but no definite conclusion has yet been arrived regarding the technique of choice for IVF. No method could be considered as superior to other technique if basic concepts pertaining to IVF are taken care. Conscious sedation is suitable for cooperative females. In addition to conscious sedation and analgesia, many methods of pain relief during oocyte recovery are currently in use. In case general anaesthesia is required, the anaesthetic drugs should be used cautiously and efforts should be made to reduce the anaesthetic duration. The preferred modality of peri-operative care should be individualized as per the requirement of the patient.

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