Review Article

Pain Management during Ultrasound Guided Transvaginal Oocyte Retrieval – A Narrative Review

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Abstract

Transvaginal oocyte retrieval (TVOR), done for the purpose of assisted reproduction can instigate enormous pain and therefore requires adequate analgesia with the least adverse effects. As the procedure involves retrieving oocytes for *in vitro* fertilisation, the effect of the anaesthetic drugs on the oocyte quality should also be considered. This review focuses on the various modes of anaesthesia and the anaesthetic drugs which can be administered safely to provide effective analgesia in normal and in special conditions such as women with pre-existing comorbidities. Medline, Embase, PubMed and Cochrane electronic databases were searched according to modified Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. According to this review, conscious sedation appears to be the most preferred mode of anaesthesia in women undergoing TVOR owing to fewer adverse effects, faster recovery, better patient and specialist comfort and the least effect on oocyte quality and embryo development. Combining it with paracervical block resulted in lesser consumption of the anaesthetic drug, which may have a beneficial effect on the oocyte quality.

Keywords: *Anaesthesia, assisted reproduction, general anaesthesia, oocyte retrieval, pain relief, regional anaesthesia*

Introduction

Assisted reproductive techniques (ARTs) in the form of *in vitro* fertilisation (IVF) or intracytoplasmic sperm injection are interventions that include *in vitro* handling of gametes or embryos for the purpose of reproduction. It is either the final recourse in many couples with unexplained infertility of long duration or the only option in women with bilateral tubal block and men with azoospermia who undergo surgical sperm retrieval. With increasing awareness and improvised techniques, the number of patients who opt for these treatment modalities is constantly on the rise. Women undergoing ART require ovarian stimulation with gonadotropins followed by oocyte retrieval. During the earlier stages of ART, oocyte retrieval was done laparoscopically. Dr. Subas Mukherjee created India's first IVF baby and the world's second IVF baby (born just 67 days after the world's first IVF baby on 3rd October 1978) by retrieving oocytes through the transvaginal approach. His great contribution was not recognised and the first reported transvaginal oocyte retrieval (TVOR) was many years later in the year 1984.[1] At present, the ultrasound-guided transvaginal approach is widely practiced for oocyte retrieval. Although the procedure is less invasive when compared to the transabdominal or laparoscopic approach, the women can experience significant pain during the procedure which demands the need for anaesthesia. This review discusses the various available methods for pain management during TVOR in women with and without associated comorbidities. The outcomes that were focused on, were pain relief during the procedure, physician and patient satisfaction, adverse effects, effect on the oocyte quality and embryo development and ART outcome. The review was written to provide insight into the methods that

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provide adequate pain relief with fewer side effects and the least impact on oocyte quality and embryo development.

Transvaginal Oocyte Retrieval and Anaesthetic Implications

Pain experienced during oocyte retrieval is due to the needle piercing the vaginal wall and stretching and piercing of the ovarian capsule. At present, conscious sedation is the most preferred method while the other practiced techniques are general anaesthesia (GA), regional or local anaesthesia.[2] Apart from providing safe analgesia with fewer adverse effects, the other major concern when it comes to anaesthesia for assisted reproduction is the presence of the anaesthetic drug in the follicular fluid and its possible effects on the oocyte quality and thereby the pregnancy rates. Follicular fluid concentration of the anaesthetic agents plays a major role in the oocyte quality, fertilisation and implantation rates. Prolonged exposure to certain agents can result in significantly lower pregnancy and live birth rates.[3] Although there have been studies on performing TVOR without analgesia, present day clinicians would prefer administering analgesia and/or anaesthesia, especially when there are drugs which are currently considered quite safe and effective.[4]

Methods

Medline, Embase, PubMed and Cochrane electronic databases were searched according to a modified Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. We included relevant articles published between the years 1987 and 2022. We have excluded animal studies and studies on anaesthesia for laparoscopic oocyte retrieval from this review.

Conscious sedation

Conscious sedation and analgesia (CSA) or procedural sedation is the most common route of anaesthesia administered for women undergoing TVOR.[5] This is the preferred mode of anaesthesia in 95% and 84% of IVF centres in the USA and UK, respectively.[2,6,7] Physician and patient satisfaction are better with CSA as most of the drugs used are also potent anxiolytics and depression in the level of consciousness is much lesser when compared to GA, thereby not necessitating assisted airway support throughout the surgical procedure.[8,9] The American College of Emergency Physicians mentions CSA as a 'technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function. CSA is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently.'[10] With meticulous administration, these drugs have the least short-term and long-term side effects, are well-tolerated and the ease of delivery is also better when compared to other modes of anaesthesia [Table 1].[6,11] A patient on CSA should be monitored as per the American Society of Anesthesiology monitoring system.

General anaesthesia

GA was the technique of choice during the earlier days of ART. The anaesthetic agents used are either intravenous; such as propofol, ketamine, opioids or benzodiazepines; or inhalational agents such as nitrous oxide (N_2O) and vapours of isoflurane, desflurane and sevoflurane [Table 2]. Isoflurane is the most commonly used drug due to its low blood gas solubility when compared to halothane and thereby has lesser central nervous system effects.[17] Patients may be kept on either spontaneous ventilation through face mask or laryngeal mask airway or mechanically ventilated through laryngeal mask airway or endotracheal tube. Apart from the less favourable effects such as prolonged recovery and post-operative nausea and vomiting, studies have also shown adverse ART outcomes such as reduced fertilisation and pregnancy rates when halogenated fluorocarbons with nitrous oxide were used.[3] The use of N_2O for GA during oocyte retrieval is controversial as many studies have shown a detrimental effect on embryos.[22] There was a recent case report on violent cough following GA with propofol and pentazocine, which resulted in ovarian haemorrhage and severe haemoperitoneum.[23] GA may be the preferred mode of anaesthesia in selected situations such as,[24]

- Anxiety or other psychological issues
- When longer procedure time or more manipulation due to the difficult procedure is expected in cases such as endometriosis/endometrioma, pelvic adhesions or difficult-to-access ovaries
- Adverse effects during conscious sedation/regional anaesthesia in previous attempts.

Literature from the earlier days of ART suggested the significant negative impact of GA on fertilisation, cleavage rates and embryo quality. There is a fair chance that the CO2 pneumoperitoneum which was created for laparoscopic oocyte retrieval could have also contributed to these findings significantly.[3,25]

Patient controlled analgesia

Although conventionally anaesthesia administration is performed by physicians, patient-controlled analgesia (PCA) offers patients control over the drug administration as per their requirements. PCA has been considered an effective alternative to physician-administered anaesthesia, especially in

Table 1: Monitored anaesthesia care, conscious sedation and analgesia, total intravenous anaesthesia

Author	Study population and design	Outcome
Bein and Klapproth 1989[12]	NA	Midazolam (0.1 mg/kg) and fentanyl (2 μg/kg) provided better anterograde amnesia along with analgesic and anxiolytic effects
Ben-Shlomo *et al*., 1999[13]	Randomised prospective study in 50 patients	Arousability was better in patients sedated with midazolam and ketamine when compared to GA with propofol, fentanyl and isoflurane, whereas oocyte retrieval rate, embryo transfers and pregnancy rates were similar in both groups
Wilhelm *et al*., 2002[14]	Retrospective data analysis of 251 patients	Pregnancy rates were better in patients who received MAC with remifentanil (30.6%) when compared to GA with alfentanil, propofol and nitrous oxide induction with isoflurane-propofol maintenance (17.9%)
Lok *et al*., 2002[15]	Prospective randomised trial in 106 patients. Patient-controlled sedation (*n*=51), Physician-administered sedation (*n*=55)	Level of sedation and co-operation was similar in both group PCS using propofol and alfentanil and PAS using diazepam and pethidine. Pain score was higher during and two h post-procedure (53±23 vs. 35±24; *P* <0.01 and 29±27 vs. 17±22; *P* <0.05, respectively) in the PCS group. Although patient satisfaction was similar in both groups, physician satisfaction was better with PAS
Fiebai *et al*., 2008[16]	Cross-sectional survey	With conscious sedation, mean pain score was low, and the pain intensity did not alter with the duration of the procedure
Murthy *et al*., 2008[17]	Retrospective analysis of records of 1496 patients	GA provided through FM with isoflurane or ETT with isoflurane, LMA with isoflurane or TIVA with propofol/fentanyl/pethidine/ morphine. Induction agents were propofol, thiopentone, ketamine or midazolam. Hemodynamic parameters were similar in all groups. Patient satisfaction was better in the TIVA group due to lesser post-operative adverse effects
Saleh *et al*., 2012[18]	Prospective randomised observer-blinded study of 60 patients	Patients who received TIVA with remifentanil and propofol had a shorter recovery time, shorter PACU and hospital stay, lesser propofol requirement and better patient satisfaction when compared to the group that received fentanyl and propofol. There was no difference in the intraoperative hemodynamic parameters, post-operative pain and adverse effects. The chemical pregnancy rate was similar 43.33% (*P*=1.000) in both groups
Matsota *et al*., 2012[19]	Randomised controlled trial including 58 women, among whom 29 patients received analgesia with remifentanil and 29 patients received anaesthesia with propofol and alfentanil	There was no significant difference in anaesthetic outcome and ART outcome in terms of number of oocytes retrieved, fertilization and cleavage rate, embryo quality, implantation rates and pregnancy rates between both groups
Tewari *et al*., 2016[20]	Prospective, randomised study involving 100 women who underwent TVOR under IV propofol. Randomised to compare drugs titrated as per entropy values: state entropy and response entropy (Group EM) and drugs titrated as per standard clinical monitoring (Group CM)	Propofol and fentanyl consumption was 6.7% lesser (*P*=0.01) and 10.9% more (*P*=0.007) in the EM group, respectively. The on-table recovery was earlier (*P*=0.009), and requirement of supplemental analgesia was also lesser (10% vs. 28.3%, *P*=0.01) in the EM group
Singhal *et al*., 2017[21]	Prospective cross-sectional study of 100 women who underwent TVOR under CSA	Post-procedure pain score increased with the duration of surgery. Otherwise, there was no correlation between number of oocytes retrieved or the transmyometrial passage of needle and the pain score. Patient satisfaction was good

TIVA=Total intravenous anaesthesia, MAC=Monitored anaesthesia care, CSA=Conscious sedation and analgesia, TVOR=Transvaginal oocyte retrieval, GA=General anaesthesia, PCS=Patient-controlled sedation, PAS=Physician-administered sedation, FM=Face mask, ETT=Endotracheal tube, LMA=Laryngeal mask airway, PACU=Post-anaesthesia care unit, ART=Assisted reproductive techniques

low-resource settings and also for patients with low ovarian reserve undergoing TVOR where the duration of the procedure may be very less [Table 3].

Regional anaesthesia

In women undergoing ART, regional anaesthesia has the advantage of minimal systemic absorption of the local anaesthetic agent and thereby very minimal follicular fluid concentration. Studies comparing regional anaesthesia with sedation and GA have not shown gross differences in anaesthetic parameters or ART outcomes [Table 4].

Paracervical and pre-ovarian block

Paracervical (PCB) and pre-ovarian block (POB) involve injecting a local anaesthetic agent adjacent to

Table 2: General anaesthesia

Author	Study population and design	Outcome
Ben-Shlomo *et al.*, 1999[13]	Randomised prospective study in 50 patients	Arousability was better in patients sedated with midazolam and ketamine when compared to GA with propofol, fentanyl and isoflurane, whereas oocyte retrieval rate, embryo transfers and pregnancy rates were similar in both groups
Hammadeh ME *et al.*, 1999[26]	Prospective comparative study in 202 women among whom 96 women opted for sedation with midazolam and diazepam/propofol and 106 opted for GA with remifentanil and propofol/isoflurane	Number of oocytes retrieved were significantly higher with GA than with sedation, whereas there was no difference in fertilization, cleavage and pregnancy rates. Authors suggested that the favourable outcome could be due to the avoidance of nitrous oxide
Wilhelm *et al.*, 2002[14]	Retrospective data analysis of 251 patients	Pregnancy rates were better in patients who received MAC with remifentanil (30.6%) when compared to GA with alfentanil, propofol and nitrous oxide induction with isoflurane-propofol maintenance (17.9%)
Murthy *et al.*, 2008[17]	Retrospective analysis of records of 1496 patients	GA provided through FM with isoflurane or ETT with isoflurane, LMA with isoflurane or TIVA with propofol/fentanyl/pethidine/ morphine. Induction agents were propofol, thiopentone, ketamine or midazolam. Hemodynamic parameters were similar in all groups. Patient satisfaction was better in the TIVA group due to lesser post-operative adverse effects

TIVA: Total intravenous anaesthesia, GA=General anaesthesia, LMA=Laryngeal mask airway, ETT=Endotracheal tube, FM=Face mask, MAC=Monitored anaesthesia care

Table 3: Patient-controlled analgesia

Author	Study population and design	Outcome
Zelcer *et al.*, 1992[27]	Prospective study in 80 women comparing physician-administered and patient- controlled alfentanil administration	The average drug requirement (1.49±0.50 and 1.46±0.55 μg/kg/min) and post-operative complications were similar in both groups. Patient comfort and satisfaction were better with PCA
Cook *et al.*, 1993[28]	Prospective randomised study where 25 patients received propofol and 22 patient received midazolam	PCA with midazolam and propofol were compared. Alfentanil was administered on demand. Onset of sedation took 70.6 s (SD 22.4) in the propofol group and 106.3 s (SD 50.7) in the midazolam group. Procedure was completed successfully and none of the patients required additional sedation
Bhattacharya *et al.*, 1997[29]	Prospective randomised study with 39 women in the PCA group and 42 women in the PAS group	Pain score was less and patient satisfaction was better in the PCA group when compared to the PAS group, whereas fentanyl utilization was significantly more in the PCA group
Thompson *et al.*, 2000[30]	Randomised controlled trial where 57 women received PCA with isodesox (1% desflurane, 0.25% isoflurane and 60% oxygen in nitrogen) and 55 women received IV fentanyl	The mean pain score was significantly lesser in the TIVA group (P=0.02), whereas a fall in oxygen saturation of less than 94% was seen in around 29% of women who received TIVA when compared to 1.7% in the PCA group
Lok *et al.*, 2002[15]	Prospective randomised trial in 106 patients. Patient-controlled sedation (n=51), Physician-administered sedation (n=55)	Level of sedation and co-operation was similar in both group PCS using propofol and alfentanil and PAS using diazepam and pethidine. Pain score was higher during and two h post-procedure (53±23 vs. 35±24, P<0.01 and 29±27 vs. 17±22, P <0.05, respectively) in the PCS group. Although patient satisfaction was similar in both groups, physician satisfaction was better with PAS
Lier *et al.*, 2015[31]	Randomised control trial involving 76 women Forty women received pethidine and midazolam-induced conscious sedation and 36 women received PCA with remifentanil and diclofenac	Pain score during the procedure was comparable for remifentanil and pethidine groups (4 [3-7] vs. 6 [4-8], P=0.13), whereas pain score was significantly lower in the CSA group (1 [0–3] vs. 2 [1–5], P=0.016). Reproductive and safety outcomes were similar, though patient satisfaction was better in the PCA group

PCA=Patient controlled analgesia, PAS=Physician-administered sedation, PCS=Patient-controlled sedation, TIVA=Total intravenous anaesthesia, SD=Standard deviation

the respective neural plexus. The paracervical block is performed under sterile conditions, with the patient in the lithotomy position. The local anaesthetic agent is injected through the cervicovaginal fornix and deposited around the cervix at four locations, usually at the 1,5,7 and 11 o'clock positions. The pre-ovarian block is performed under ultrasound guidance, by infiltrating the local anaesthetic agent in the vaginal wall and peritoneal surface adjacent to the ovary [Table 5].

Table 4: Regional anaesthesia-spinal anaesthesia, epidural anaesthesia

Author	Study population and design	Outcome
Manica *et al.*, 1993[32]	Randomized study of 56 women, comparing SA with 1.5% and 5% hyperbaric lidocaine in combination with 10 µg of fentanyl	The sensory level, maximum motor block, requirement for additional IV sedation, time to two-segment regression and time to full sensory recovery were similar in both groups. Recovery time in terms of time to ambulation (141±21 min vs. 162±29 min; *P*<0.05), time to void (147±21 min vs. 174±28 min; *P*<0.05), time to achieve full motor recovery (86±21 min vs. 111±22 min, *P*<0.0001), and discharge time (170±38 min vs. 201±41 min, *P*<0.05) was significantly shorter in women who received 1.5% lidocaine
Botta *et al.*, 1995[33]	Study comparing 50 oocyte retrievals done under EA and 112 retrievals done under IV propofol with nitrous oxide mask ventilation	Fertilisation, cleavage and pregnancy rates were similar in both groups (67.2%, 92% and 20% in the EA group and 69.3%, 93% and 19.6% in the IV sedation group. Post-operative nausea and vomiting were significantly higher in the IV sedation group
Viscomi *et al.*, 1997[34]	Retrospective pilot study involving 95 women who underwent TVOR under TIVA (*n*=44) or SA (*n*=51)	ART outcome was similar in both groups. The time to discharge (P=0.03), and post-operative side effects such as vomiting (46% vs. 6%, *P*<0.01) was significantly higher in the TIVA group
Guasch *et al.*, 2005[35]	Ninety women were randomized into 4 groups to receive either GA, SA, CSA with alfentanil + midazolam+PCB or CSA with remifentanil+PCB	Plasma levels of prolactin and cortisol were compared in all four groups. Prolactin levels were highest in patients receiving GA. There was complete attenuation of increase in prolactin level in women who received SA
Piroli *et al.*, 2012[36]	Retrospective analysis comparing local anaesthetic agent EMLA cream (lidocaine 2.5% and prilocaine 2.5%), propofol, sevoflurane and thiopental sodium	Analgesia and hemodynamic parameters were similar in all groups. Both EMLA and sevoflurane groups resulted in higher yield of MII oocytes and better fertiliation rate when compared to the propofol and thiopental sodium groups (*P*<0.001)
Azmude *et al.*, 2013[37]	Randomized clinical trial involving 200 women, randomly allocated to receive either GA (*n*=100) or SA (*n*=100)	Pregnancy rates were significantly higher in the SA group (27%) when compared to the GA group (15%), *P*<0.001
Aghaamoo *et al.*, 2014[38]	Retrospective analysis of case records comparing GA and SA for TVOR in terms of achieving a chemical pregnancy	The chance of achieving chemical pregnancy (positive pregnancy test) was significantly higher in women who received SA (adjusted OR=2.07, 95% CI: 1.02,4.20, *P*=0.043)
Heo *et al.*, 2020[39]	Retrospective analysis of records of 95 patients who underwent TVOR under SA (*n*=77) or MAC (*n*=18)	The pregnancy rates were similar in both groups (32.5% in the SA group and 33.3% in the MAC group, *P* - 0.575). Time taken for the procedure was significantly longer in the MAC group (*P*<0.001).

TVOR=Transvaginal oocyte retrieval, TIVA=Total intravenous anaesthesia, MAC=Monitored anaesthesia care, GA=General anaesthesia, PCB=Paracervical, CSA=Conscious sedation and analgesia, ART=Assisted reproductive techniques, CI=Confidence interval, OR=Odds ratio, EA=Epidural anaesthesia, SA=Spinal anaesthesia, EMLA=Eutectic mixture of local anaesthetics, MII oocyte=Metaphase II oocyte

Drugs

Drugs used for anaesthesia and their dosage plays a major role in the anaesthetic management as well as the ART outcome [Table 6]. For providing sedation, most anaesthesiologists prefer midazolam and/or propofol with fentanyl. Choosing the right drug is extremely important as it not only involves patient safety, but the outcome may also be affected if the drug accumulates in the follicular fluid. Midazolam is the most preferred benzodiazepine due to its potent sedative and anxiolytic properties. When combined with opioids, the synergistic action is known to provide better analgesic effect.[8] The combined action also necessitates lesser dose requirement for both drugs. A randomized trial published in 2008 concluded that side effects were lesser with midazolam and fentanyl combination when compared to propofol and fentanyl.[57] While considering opioid administration, remifentanil has proved to be better than fentanyl in terms of faster recovery.[58]

Propofol is used both for conscious sedation as well as GA. It has both sedative and analgesic properties and the advantage of faster onset, short elimination time and lesser incidence of post-operative nausea and vomiting.[17] Daycare procedures such as TVOR require drugs with a shorter half-life which aids in rapid weaning from anaesthesia. Both patient and physician satisfaction are better when there is early awakening and orientation to time with quick return of normal psychomotor performance. The rapid metabolisation of propofol in the liver aids in accelerated clearance from the system and thereby faster recovery when compared to other intravenous anaesthetic agents.[17] There is a dose-dependent incidence of respiratory and myocardial depression with propofol, which can be overcome by

Table 5: Paracervical and pre-ovarian block

Author	Study population and design	Outcome
Wikland *et al.*, 1990[40]	Comparative study of 46 women who received PCB with lidocaine 50 mg and 46 women who did not	The mean follicular fluid concentration of lidocaine was 0.36±1.1 µg/mL. The fertilisation rate did not vary in oocytes retrieved from follicles containing lidocaine in their fluid. The fertilisation, cleavage and pregnancy rates were similar in both groups
Corson *et al.*, 1994[41]	Prospective, randomized, double-blinded, placebo-controlled study involving 101 women who received IV sedation, randomly allocated to either receive PCB or not	Patient and physician-assessed pain scores were lesser in the group that received the PCB along with the IV sedation
Christiaens *et al.*, 1998[42]	Prospective study comparing GA with propofol and PCB in 202 women	The fertilisation, cleavage, implantation and ongoing pregnancy rates were similar in both groups
Ng *et al.*, 1999[43]	Prospective, double-blinded, placebo-controlled study on 135 women, randomly allocated to receive 10 ml of 1.5% lignocaine (group A) or normal saline (group B) in the PCB and no local injection (group C)	The procedure duration, number of follicles punctured and pregnancy rates were similar in all groups. Though vaginal puncture pain score was similar in all groups, abdomen pain was significantly lesser by 40%–50% in group A when compared to the other groups
Ng *et al.*, 2000[44]	Prospective, double-blinded study on 150 women, randomised to receive either 200 mg or 150 mg lignocaine in the PCB	The fertilisation, implantation and pregnancy rates were similar in both groups. The median pain levels during vaginal punctures and abdominal pain were similar in both groups. Therefore, 150 mg of lignocaine seemed to be satisfactory for the procedure
Ng *et al.*, 2001[45]	Prospective double-blinded study of 150 women, randomised to receive either PCB alone or PCB with conscious sedation	Level of vaginal and abdominal pain was 2.5 times higher in women who received only PCB
Ramzy *et al.*, 2001[46]	Prospective, randomised study to evaluate post-operative pain relief by administration of sub-ovarian capsule and vaginal puncture site local anaesthetic. Seventy-two women underwent TVOR under IV sedation, randomised to receive lignocaine (Group A, *n*=24), normal saline (Group B, *n*=24), or no intervention (Group C, *n*=24) after TVOR	Post-operative analgesic requirement was similar in all groups, (Group A-41.7%, Group B-41.7%, in Group C-29.2%). Subcapsular local anaesthetic administration did not prove useful
Ng *et al.*, 2003[47]	Prospective, double-blinded study on 153 women under IV sedation, randomised to receive three different doses of either 50, 100 and 150 mg lignocaine in the PCB	Vaginal and abdominal pain levels during and 4 h after the procedure were not significantly different among the three groups. Therefore, authors recommend the use of 50 mg of lignocaine for PCB
Tummon *et al.*, 2004[48]	Randomised trial comparing use of use of lidocaine gel or PCB with lidocaine in adjunct to IV sedation	Pain experience was more in the group on lidocaine vaginal gel when compared with lidocaine PCB
Öztürk *et al.*, 2006[49]	Prospective comparative study of two groups (*n*=100) receiving either TIVA with remifentanil infusion alone or in combination with PCB	Haemodynamic and respiratory parameters were similar in both groups. Pain score, remifentanil requirement and post-operative nausea and vomiting was significantly higher in the group that received remifentanil alone (P<0.05)
Atashkhoii 2006[50]	Prospective randomised double-blinded study. Sixty-women were randomised to receive either CSA alone (Fentanyl + Midazolam + Propofol) or CSA with PCB	Vaginal and abdominal pain were significantly lesser in the CSA + PCB group. Propofol requirement was also significantly lesser in the PCB group (8.67±2.42 mg) when compared to CSA alone (25.60±5.29 mg), P<0.0005. Incidence of intraoperative and post-operative adverse effects were significantly lesser in the CSA + PCB group
Cerne *et al.*, 2006[51]	Prospective, multicentre study, where 183 women were randomised to receive POB (*n*=96) or PCB (*n*=87)	The pain score, level of anxiety, alfentanil requirement, fertilisation rate, number of good-quality embryos and clinical pregnancy rates were similar in both groups
Gunaydin *et al.*, 2007[52]	Randomised controlled trial involving 40 women, randomly allocated to receive either remifentanil infusion alone (*n*=20) or with PCB (*n*=20)	Plasma remifentanil concentration and pulmonary function was compared in both groups. Haemodynamic and respiratory parameters were similar in both groups. Remifentanil requirement and therefore plasma remifentanil concentration was significantly higher when adjuvant PCB was not given (P<0.05)
Milanini *et al.*, 2008[53]	Retrospective study comparing local anaesthesia with continuous IV remifentanil	Number of oocytes retrieved were more and the procedure was more comfortable in the IV remifentanil group

Contd...

Table 5: Contd...

Author	Study population and design	Outcome
Bumen *et al.*, 2011[54]	Prospective randomised study comparing TIVA with remifentanil + propofol with PCB	Fertilisation rate was similar in both groups. Though the number of retrieved and mature oocytes, embryo numbers and pregnancy rate were higher in the TIVA group, only the increased number of embryos was statistically significant (P=0.045)
Oliveira *et al.*, 2016[55]	Randomised double-blinded clinical trial involving 61 women who were randomly allocated to receive 1mcg/kg of fentanyl with 1.5 mg/kg of propofol (n=32), or 0.075mg/kg of midazolam with 0.25mcg/kg/min of remifentanil, and paracervical block with 3 mL of 2% lidocaine (n=29)	Haemodynamic and anaesthetic parameters were similar in both groups. Though pregnancy rate was higher in the fentanyl/propofol group (44% vs. 22%), it was not statistically significant
Rolland *et al.*, 2017[56]	Non-randomised prospective cohort study, where 234 women received PCB and 247 women received GA	Post-operative vaginal and abdominal pain was significantly more in the PCB group when compared to the GA group (2.26±0.159 vs. 1.66±0.123, respectively, P=0.005, and 3.80±0.165 vs. 3.00±0.148, respectively, P<0.001). Therefore, patient satisfaction was also significantly more in the GA group, (P<0.001). Whereas, the live birth rates were similar in both groups (19.8% in the GA group vs. 20.9% in the PCB group, P=0.764)

GA=GA=General anaesthesia, PCB=Paracervical, TIVA=Total intravenous anaesthesia, POB=Pre-ovarian block, CSA=Conscious sedation and analgesia, TVOR=Transvaginal oocyte retrieval

combined administration of an opioid such as fentanyl. The follicular fluid concentration of propofol was also found to be dose-dependent.[59] There was no difference in ART outcome in terms of fertilisation, cleavage, implantation or abortion rates when compared with thiopental. Propofol requirement was found to more in patients who were highly anxious before the procedure.[60]

Ketamine belongs to the phencyclidine family of drugs and causes dissociative anaesthesia through a central neurological action. Due to its additional properties such as analgesic effect, loss of consciousness and anterograde amnesia without cardiorespiratory depression, it was once considered an ideal anaesthetic agent, both for GA and conscious sedation. Yet, the drug lost its popularity due to its undesirable post-operative effects such as vivid dreaming, illusions and feelings of fear or excitement which persist for considerable several hours.

Other interventions

Various other modalities such as electroacupuncture and acupressure have also been suggested for pain management during oocyte retrieval.[87,88] Although these techniques have provided better pain relief when combined with intravenous sedation, they have not been quite helpful as a stand-alone treatment for intra-or post-operative pain relief.[89] Simple and inexpensive interventions such as music therapy can also reduce pain scores and patient anxiety and improve patient satisfaction.[90] A booklet for coping intervention for oocyte retrieval was developed by a psychologist. The booklet has information about the oocyte retrieval procedure in detail, including pain and possible outcomes and coping strategies such as muscle relaxation, distraction techniques, deep breathing and positive reappraisal. These coping strategies may also improve patient satisfaction and recovery.[91]

Special Considerations

Comorbidities

Patients should be evaluated for co-existing medical conditions before the administration of anaesthesia. With increasing age at conception and fertility treatment, it is crucial to evaluate women for possible associated medical conditions such as diabetes, hypertension and heart disease. Moreover, subfertile women may also have associated hypothyroidism, obesity, diabetes or hypertension or a history of tuberculosis or severe acute respiratory syndrome (SARS) COVID-19 in the past. They may be on drugs not only for the above-mentioned conditions but may also be on anticoagulants or psychiatric medications. All of these should be taken into consideration before deciding on the drug, the route of administration and the intra-operative and post-operative monitoring protocol. Special care should be taken for cancer patients who have presented for fertility preservation. Lately, ART is being done solely for the purpose of pre-implantation genetic testing for monogenic disorders. Patients undergoing the procedure may have conditions such as myotonic dystrophy, Marfan's syndrome or neurofibromatosis, which can influence the anaesthetic management and post-operative recovery.[92]

Anti-coagulant and anti-platelet use

Women with recurrent pregnancy loss due to antiphospholipid antibody syndrome may be on low-molecular-weight heparin injections and aspirin. Aspirin may be continued, whereas the last dose

Table 6: Drugs

Author	Study population and design	Outcome
	CSA/TIVA/MAC	
Endler *et al.*, 1987[61]	Prospective study comparing follicular fluid level of thiopental (*n*=15) and thiamylal (*n*=9)	The mean plasma concentration of thiamylal was 7.99±3.97 µg/mL and thiopental was 4.13±0.90 mcg/ml. Though the mean follicular fluid concentration of the drugs were similar (thiopental 1.62±0.61 µg/mL; thiamylal 1.67±0.83µg/mL), the mean FF/plasma concentration ratio was greater in the thiopental group (0.41±0.19) when compared with the thiamylal group (0.22±0.14)
Shapira *et al.*, 1991[62]	Prospective double-blinded study of 36 women, where 19 women received alfentanil up to 0.025 mg/kg and 17 received fentanyl up to 0.0025 mg/kg	Duration of procedure, analgesic effect and pregnancy rates were similar in both groups. When compared to fentanyl (3.4±2.2 min), induction was significantly shorter with alfentanil (1.3±0.7 min). Post-procedure drowsiness was also less with alfentanil
De Amici *et al.*, 1992[63]	Studied safety of continuous IV infusion of propofol for TVOR	Authors observed that the haemodynamic and respiratory parameters were stable, there were no adverse effects and regaining psychomotor functions were rapid
Coetsier *et al.*, 1992[59]	Studied follicular fluid concentration of propofol in 9 patients	Follicular fluid propofol levels showed a steady increase and it was time dependent
Soussis *et al.*, 1995[64]	Clinical trial in 28 women, 15 of whom received midazolam and fentanyl and 13 received midazolam and alfentanil	Both plasma and follicular fluid levels of the agents administered were monitored. Follicular fluid levels increased significantly up to 25 minutes after administration of the agents. Fertilisation and pregnancy rates were similar in all groups, but patient numbers were small
Shapira *et al.*, 1996[62]	Observational study conducted on 14 women to determine serum and follicular fluid alfentanil concentration	Follicular fluid level of alfentanil (8.9±0.8 ng/mL at 15 min) was significantly lesser than the serum level (92±20 ng/mL at 5 min)
Casati *et al.*, 1999[65]	Randomised clinical trial of 60 women, randomly allocated to receive either propofol and fentanyl or midazolam and remifentanil	Need for manual ventilation was more frequent in the propofol/fentanyl group when compared to the midazolam/remifentanil group (50% vs. 30%, *P*<0.05) and the time to achieve an Aldrete's score of 10 was also shorter in the midazolam and remifentanil group
Ben-Shlomo *et al.*, 2000[66]	Prospective cohort study of 130 women who had TIVA with propofol and fentanyl	Even though there was an increase in the follicular fluid concentration of propofol with time, there was no difference in the oocyte maturity, quality, fertilisation, cleavage rates or embryo numbers for the first and last retrieved oocytes as per elapsed procedure time
Huang *et al.*, 2000[67]	Retrospective comparative study of GA with propofol (*n*=72) and thiopental sodium (*n*=20)	The fertilisation and cleavage rates were similar in propofol and thiopentone groups (68.9 vs. 66.7% and 96.5 vs. 94.8%, respectively). Embryo quality, pregnancy, implantation and miscarriage rates were also similar in both groups
Ma *et al.*, 2008[57]	Randomised control trial in 80 patients receiving conscious sedation who were randomly assigned to receive either midazolam with fentanyl or propofol with fentanyl	Analgesic effect and haemodynamic parameters were similar in both groups, but midazolam when combined with fentanyl was found to better in terms of lesser incidence of respiratory depression (5% vs. 25%), post-operative vomiting (10% vs. 27.5%) and better amnesia (25% vs. 7.5%)
Coskun *et al.*, 2011[68]	Randomised control trial involving 69 women who received remifentanil at varying doses. They were randomly allocated into three groups consisting of 23 patients who received either 1.5, 2.0 or 2.5 ng/mL of remifentanil	Haemodynamic parameters, level of sedation and pain scores were similar in all three groups, whereas recovery was earlier in the groups which received 1.5 or 2.0 ng/mL
Sarikaya *et al.*, 2011[69]	A double-blinded prospective randomised controlled trial involving 86 women. Group 1 received remifentanil dose of 0.1 µg/kg/min while Group 2 received 0.15 µg/kg/min infusion	Haemodynamic parameters and patient satisfaction was similar in both groups. Anaesthesiologist satisfaction was better in group 1 (*P*=0.009) whereas surgeon satisfaction was better in group 2 (*P*=0.01). There was no difference in fertilisation, cleavage or pregnancy rates
Jarahzadeh *et al.*, 2011[58]	Double-blinded randomised clinical trial of 145 women, comparing monitored anaesthesia care with remifentanil and fentanyl, preceded by induction with thiopental	Recovery from anaesthesia and pregnancy rates were better in the remifentanil group when compared to the fentanyl group

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Table 6: Contd...

Author	Study population and design	Outcome
	CSA/TIVA/MAC	
Liang *et al.*, 2011[70]	Randomised controlled trial of 81 women to assess the efficacy of subclinical doses of 0.4 mg/kg of pentazocine with 1.5 mg/kg propofol and 0.5 mg/kg pentazocine with 1.5 mg/kg propofol	The analgesic effect, propofol requirement, adverse effects, unconsciousness time, awake time and hospital stay were similar in both groups. Intraoperative consciousness and need for increasing propofol dose was more in the group which received the subclinical dose
Goutziomitrou *et al*. 2015[71]	Randomised controlled trial comparing IV sedation with propofol (*n*=90) and thiopental sodium (*n*=90)	Number of oocytes retrieved, overall fertilisation rates and fertilisation rates for ICSI were similar in both groups. Though live birth rate was higher in the propofol group, there was no statistical significance. The time under anaesthesia was significantly more in the thiopental sodium group when compared to the propofol group: median (IQR): 12 (5) versus 10 (4.5) min, *P*=0.019
Elnabtity and Selim 2017[72]	Prospective randomised double-blinded trial involving 52 patients who were equally allotted to receive either dexmedetomidine or midazolam for conscious sedation. All received an initial loading dose of fentanyl and a paracervical block	Pain score was significantly lesser in the dexmedetomidine group when compared to the midazolam group both intra-operatively and at 20 min during PACU time. Although there was significant bradycardia in the dexmedetomidine group, the need for rescue sedation and PACU stay time was also significantly lesser in this group
Morue *et al.*, 2018[73]	Randomised controlled, prospective, double-blinded study of 132 women out of which 121 completed the study. One group received a ketamine infusion (40 µg kg min over 5 min followed by 2.5 µg kg min) and the other, a 0.9% saline infusion in addition to the variable remifentanil TCI	There was no episode of respiratory depression in both groups and no patient required ventilatory support. Pain score and remifentanil concentrations were reduced significantly in the ketamine group, but the latter remained above 2 ng ml. The incidence of post-operative nausea was lesser in the ketamine group, but it did not influence length of stay nor patient satisfaction
Tola 2019[74]	Retrospective analysis of records of 333 women. They were evaluated under three groups depending on whether they received propofol (*n*=217), or ketamine (*n*=60), or propofol and ketamine (*n*=56)	Fertilisation rates were lesser in the ketamine group, whereas implantation, clinical pregnancy and live birth rates were similar in all groups. An extended duration of anaesthesia of more than 30 min was associated with lower implantation and clinical pregnancy rates
Farzi *et al.*, 2019[75]	Double-blinded clinical trial. Three hundred and forty patients were randomly allocated to receive alfentanil (A; 15 µg/kg), fentanyl (F; 1.5 µg/kg) or remifentanil (R; 1.5 µg/kg). One hundred and five women were lost to follow up	Time to respond to verbal command was significantly more in the fentanyl group (A: 1.99±1.64, *F*: 2.56±1.72, *R*: 1.78±1.34, *P*=0.014). Intensity of post-operative pain and patient satisfaction were similar in all groups. Although the implantation, biochemical and chemical pregnancy rates were similar in the groups, the fertilisation rate was significantly lesser in the alfentanil group when compared to the others (A: 51.6%, *F*: 54.4%, *R*: 62.2%, *P*=0.018)
Matsota *et al.*, 2021[76]	Prospective cohort study of 72 cycles/patients where group 1 received dexmedetomidine and fentanyl and the group 2 received remifentanil and midazolam	Propofol consumption was significantly higher in group 1 when compared to group 2 (77.0±10.6 mg vs. 12.1±6.1; *P*<0.001). Post-anaesthesia discharge score was better in group 2 (15.0 vs. 5.0 min, *P*=0.028). Fertilisation rates were similar in both groups whereas quality of embryos on day 3 was better in group 1
Orak *et al.*, 2021[77]	A prospective, randomised and controlled trial with 60 patients. Patients were randomly allocated into two groups of 30 patients each. Group 1 received remifentanil and propofol and Group 2 received remifentanil and sevoflurane	Neuroendocrine stress response was evaluated with the help of certain blood parameters. In group 1 ACTH, glucagon, and PGE2 increased post-operatively, while cortisol decreased. In group 2 aldosterone and CRH increased post-operatively. Post-operative levels of Glucagon and PG E2 were higher in group 1 when compared to group 2
Saravanaperumal and Udhayakumar 2021[78]	Prospective randomised control study of 66 patients. They were randomised into two equal groups who received TIVA with either dexmedetomidine and propofol or fentanyl and propofol	Dexmedetomidine and propofol combination provided statistically better quality of recovery, lesser requirement of rescue analgesia and lesser incidence of post-operative nausea and vomiting

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Table 6: Contd...

Author	Study population and design	Outcome
	CSA/TIVA/MAC	
	General anaesthesia	
Handa-Tsutsui and Kodaka 2007[79]	Randomised prospective study of 47 women to determine the target concentration of propofol needed to prevent movement in 50% (Cp50) and 95% (Cp95) of women and whether nitrous oxide supplementation had an influence on the same	Addition on 50% nitrous oxide significantly reduced the Cp50 value for target controlled infusion of propofol by a factor of 1.24 (95% CI: 1.07–1.44)
	Spinal anaesthesia	
Martin *et al.*, 1999[80]	Randomised clinical trial where 78 women were randomly allocated to receive spinal anaesthesia with 45 mg of hyperbaric 1.5% lidocaine with or without additional 10 mcg of fentanyl	Intraoperative (P<0.05) and post-operative (P<0.0005) VAS pain scores, and post-operative narcotic requirement (P<0.005) were significantly lower in the fentanyl group. The other variables such as time to ambulation, urination and discharge were similar in both groups
Tsen *et al.*, 2001[81]	Prospective double-blinded clinical trial of 40 women, randomised to receive either intrathecal hyperbaric bupivacaine 3.75 mg (0.5 mL of 0.75%) with fentanyl 25 µg or hyperbaric lidocaine 30 mg (2.0 mL of 1.5%) with fentanyl 25 µg	Though time to onset and recovery of sensory and motor function was similar in both groups, time taken to void and hospital stay were significantly longer in the bupivacaine group. Some patients required intravenous analgesic supplementation in both groups
	Paracervical block	
Godoy *et al.*, 1993[82]	Randomised clinical trial comparing paracervical block with mepivacaine 1% (n=46) and prilocaine 1% (n=54)	When combined with standard pre-medication, both the local anaesthetic agents were equally effective in reducing pain during TVOR, but Mepivacaine was preferred over prilocaine due to the risk of methaemoglobinaemia
	Local anaesthetic	
Shao *et al.*, 2020[83]	Prospective study of patients who underwent TVOR, comparing addition of vaginal topical tetracaine to intravenous propofol (n=53) and propofol alone (n=48)]	Tetracaine when combined with propofol anaesthesia effectively reduced the propofol requirement, post-operative pain and better surgeon and patient satisfaction
	Pre-medication	
Ng *et al.*, 2002[84]	Randomised double-blinded controlled trial. Hundred women were randomised to either receive the pre-medication (50 mg pethidine and 25 mg promethazine) or placebo (normal saline intramuscularly) 30 min prior to TVOR	There was no difference in procedure duration, number of follicles punctured and clinical outcome. Pre-operative anxiety level, level of vaginal and abdominal pain during TVOR and 4 h after the procedure was significantly higher in the placebo group. Patients who received pre-medication complained of persistent drowsiness post-procedure
	Post-operative pain relief	
Sacha *et al.*, 2022[85]	Randomised double-blinded, placebo controlled trial comparing post-operative pain scores in women who were randomly allocated to receive Group A - 1000 mg of IV acetaminophen + PO placebo, Group B-IV placebo + 1000 mg PO acetaminophen, Group C-IV and PO placebo	Mean pain score and ART outcome was similar in all three groups. Post-operative opioid requirement was lesser in Group A when compared to Groups B and C (0.24 vs. 0.59 vs. 0.58 mg IV morphine equivalents, respectively)
	Analgesics	
Seidler *et al.*, 2021[86]	Retrospective cohort study of women receiving a single 30 mg of intravenous ketorolac intraoperatively (n=1780) compared to women who did not receive the drug (n=826)	Need for post-operative narcotics was significantly lesser in the ketorolac group when compared to the non-ketorolac group (12% vs. 25%). There was no significant difference in the clinical pregnancy rate

TVOR=Transvaginal oocyte retrieval, ART=Assisted reproductive techniques, CI=Confidence interval, PACU=Post-anaesthesia care unit, IQR: Interquartile range, PG=Prostaglandin, CRH=Corticotropin releasing hormone, ACTH=Adrenocorticotropic hormone

of heparin should be given at least 12 h before the procedure and the post-procedure dose should be administered 24 h later.[93]

Severe acute respiratory syndrome coronavirus 2

Patients were not taken up for ART during the initial days of the COVID-19 pandemic. When services resumed, ART procedures were done while abiding to the COVID-19 protocol. In our personal experience, patients were tested for the SARS coronavirus 2 infection before TVOR, and the procedure was cancelled if the result showed a positive status. In exceptional situations such as ovarian hyperstimulation syndrome (OHSS) or fertility preservation, it was decided to proceed with the TVOR

after explaining the benefits and risks to the patient. As far as anaesthesia was concerned, both conscious sedation with analgesia and regional anaesthesia proved to be a safe option in these patients.[94] Cycle cancellation involves both mental and financial strain on the patient, especially in the Indian setting, where patients cannot avail of insurance for ART services.

Ovarian hyperstimulation syndrome

OHSS is one of the most dreaded complications of assisted reproduction. The supraphysiological hormone levels from the hyperstimulated and enlarged ovaries lead to the production of excessive inflammatory mediators including vasoendothelial growth factor. These changes ultimately result in increased capillary permeability and a shift of intravascular fluid to the third space. Although it is quite unusual for these changes to happen before oocyte retrieval, there are reports of the onset of symptoms within 24 h of administration of hCG.[95] Patients may present with complications ranging from varied levels of ascites to hypotension, hydrothorax or even pulmonary oedema and shock. These women require rapid-sequence induction for endotracheal intubation and airway protection. Fluid management must be meticulous and patients may require an arterial or central venous line for both fluid administration and adjustment to maintain perfusion and avoid fluid overload and consequences due to increased capillary permeability. In case of extensive ascites or hydrothorax, paracentesis or thoracocentesis may be planned before the administration of GA to improve the respiratory reserve.[96]

Discussion

This review includes research articles on all modalities of pain relief administered during TVOR. There was no strong evidence to prove that a particular anaesthetic technique was better than the rest. Conscious sedation provided better patient and physician satisfaction due to faster recovery and lesser adverse effects when compared to GA.[13,14] Although the ART outcome was similar in both groups, some studies have shown a negative effect when nitrous oxide was used.[14] Similarly, the administration of opioids along with CSA or GA was found to be beneficial with regard to recovery, adverse effects and ART outcome.[8] Intraoperative pain was significantly higher with PCA when compared to the other modalities, although there was no difference in pregnancy rates.[15,31] Paracervical block alone may not provide adequate pain relief unless it is combined with another modality such as conscious sedation[45] or GA,[56] whereas remifentanil[49] or propofol[50] when combined with PCB provides better pain relief and also reduces the requirement of the anaesthetic drug. Various doses of lignocaine have been tried and 50 mg of lignocaine for PCB has proven to be effective in managing pain.[47]

Post-operative side effects such as nausea and vomiting are common with GA or CSA when compared to regional anaesthesia.[33] A recent Indian study suggested that the incidence of nausea and vomiting was more with the use of opioids and that the use of dexmedetomidine instead of fentanyl improved symptoms.[78] Studies have not compared regional anaesthesia with GA or CSA in terms of ambulation, but the use of 1.5% lidocaine resulted in earlier ambulation when compared to 5% lidocaine,[32] whereas the addition of fentanyl to 1.5% lidocaine did not alter the time to ambulation.[80] In our experience, both physicians and patients prefer CSA or TIVA when compared to EA/SA for earlier ambulation and lesser duration of hospital stay. Although GA may provide the best pain relief, disadvantages such as prolonged recovery, need for assisted ventilation, post-operative side effects and the cost factor makes it less favourable when compared to CSA.

Although the review is a compilation of the available evidence for pain relief, statistical analysis was not done to pool the evidence due to the heterogeneity of the studies, different study designs, comparators, dosage and types of drugs. Moreover, the ART outcome also depends on numerous variables and is not confined to the mode of anaesthesia and the anaesthetic drugs alone.

Conclusion

In recent times, both patient and specialist prefer an anaesthetic modality which provides early recovery with the least adverse effects. For TVOR especially, women prefer alternatives to GA for faster recovery, cost-effectiveness or for the fear of anaesthesia.[97,98] No single technique or drug has been identified as the best choice for TVOR. Yet, it is the duty of the physician and the anaesthesiologist to individualise and identify the best suitable modality for every woman, discuss the available techniques and the reason for suggesting a particular modality for her, its advantages and possible adverse effects. According to this review, conscious sedation appears to be the most preferred mode of anaesthesia in women undergoing TVOR owing to its fewer adverse effects, faster recovery, better patient and specialist comfort and the least effect on oocyte quality and embryo development. Combining it with paracervical block resulted in lesser consumption of the anaesthetic drug, which may have a beneficial effect on the oocyte quality. Therefore, a multimodal approach may be able to provide effective pain relief and better recovery with fewer adverse effects.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bharadwaj A. The Indian IVF saga: A contested history. Reprod Biomed Soc Online 2016;2:54-61.
2. Vlahos NF, Giannakikou I, Vlachos A, Vitoratos N. Analgesia and anesthesia for assisted reproductive technologies. Int J Gynaecol Obstet 2009;105:201-5.
3. Hayes MF, Sacco AG, Savoy-Moore RT, Magyar DM, Endler GC, Moghissi KS. Effect of general anesthesia on fertilization and cleavage of human oocytes *in vitro*. Fertil Steril 1987;48:975-81.
4. Ramsewak SS, Kumar A, Welsby R, Mowforth A, Lenton EA, Cooke ID. Is analgesia required for transvaginal single-follicle aspiration in *in vitro* fertilization? A double-blind study. J In Vitro Fert Embryo Transf 1990;7:103-6.
5. Benzoni T, Cascella M. Procedural sedation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551685/. [Last accessed on 2021 Oct 21].
6. Ditkoff EC, Plumb J, Selick A, Sauer MV. Anesthesia practices in the United States common to *in vitro* fertilization (IVF) centers. J Assist Reprod Genet 1997;14:145-7.
7. Elkington NM, Kehoe J, Acharya U. Intravenous sedation in assisted conception units: A UK survey. Hum Fertil (Camb) 2003;6:74-6.
8. Tobias JD, Leder M. Procedural sedation: A review of sedative agents, monitoring, and management of complications. Saudi J Anaesth 2011;5:395-410.
9. Trout SW, Vallerand AH, Kemmann E. Conscious sedation for *in vitro* fertilization. Fertil Steril 1998;69:799-808.
10. Green SM, Roback MG, Krauss BS, Miner JR, Schneider S, Kivela PD, *et al.* Unscheduled procedural sedation: A multidisciplinary consensus practice guideline. Ann Emerg Med 2019;73:e51-65.
11. Acharya U, Elkington N, Manning L, Thorp-Jones D, Tavener G. Recommendations for good practice for sedation in assisted conception. Hum Fertil (Camb) 2020;23:150-8.
12. Bein T, Klapproth CE. Analgosedation with midazolam and fentanyl as an alternative to general anesthesia in transvaginal follicle puncture within the scope of *in vitro* fertilization. Anasth Intensivther Notfallmed 1989;24:77-80.
13. Ben-Shlomo I, Moskovich R, Katz Y, Shalev E. Midazolam/ketamine sedative combination compared with fentanyl/propofol/isoflurane anaesthesia for oocyte retrieval. Hum Reprod 1999;14:1757-9.
14. 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.
15. Lok IH, Chan MT, Chan DL, Cheung LP, Haines CJ, Yuen PM. A prospective randomized trial comparing patient-controlled sedation using propofol and alfentanil and physician-administered sedation using diazepam and pethidine during transvaginal ultrasound-guided oocyte retrieval. Hum Reprod 2002;17:2101-6.
16. Fiebai PO, Ogunmokun AA, Ajayi RA. Experience with conscious sedation for oocyte retrieval in Nigeria. Afr J Reprod Health 2008;12:30-4.
17. Murthy T, Gupta P, Sharma RK. Anaesthetic issues in *in-vitro* fertilisation. Med J Armed Forces India 2008;64:119-22.
18. Saleh SE, Elshmaa NS, Ismail MT. A comparison of two different regimens of total intravenous anesthesia for transvaginal ultrasound-guided oocyte retrieval. Middle East Fertil Soc J 2012;4:256-61.
19. Matsota P, Sidiropoulou T, Batistaki C, Giannaris D, Pandazi A, Krepi H, *et al.* Analgesia with remifentanil versus anesthesia with propofol-alfentanil for transvaginal oocyte retrieval: A randomized trial on their impact on *in vitro* fertilization outcome. Middle East J Anaesthesiol 2012;21:685-92.
20. Tewari S, Bhadoria P, Wadhawan S, Prasad S, Kohli A. Entropy vs. standard clinical monitoring using total intravenous anesthesia during transvaginal oocyte retrieval in patients for *in vitro* fertilization. J Clin Anesth 2016;34:105-12.
21. Singhal H, Premkumar PS, Chandy A, Kunjummen AT, Kamath MS. Patient experience with conscious sedation as a method of pain relief for transvaginal oocyte retrieval: A cross sectional study. J Hum Reprod Sci 2017;10:119-23.
22. Gonen O, Shulman A, Ghetler Y, Shapiro A, Judeiken R, Beyth Y, *et al.* The impact of different types of anesthesia on *in vitro* fertilization-embryo transfer treatment outcome. J Assist Reprod Genet 1995;12:678-82.
23. Okoshi C, Takahashi T, Ota K, Suganuma R, Fujimori K. Severe hemoperitoneum after oocyte retrieval due to ovarian hemorrhage possibly caused by violent cough under general anesthesia with propofol and pentazocine: A case report and literature review. Cureus 2021;13:e18724.
24. ESHRE Working Group on Ultrasound in ART, D'Angelo A, Panayotidis C, Amso N, Marci R, Matorras R, *et al.* Recommendations for good practice in ultrasound: Oocyte pick up(†). Hum Reprod Open 2019;2019:hoz025.
25. Boyers SP, Lavy G, Russell JB, DeCherney AH. A paired analysis of *in vitro* fertilization and cleavage rates of first- versus last-recovered preovulatory human oocytes exposed to varying intervals of 100% CO2 pneumoperitoneum and general anesthesia. Fertil Steril 1987;48:969-74.
26. 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.
27. Zelcer J, White PF, Chester S, Paull JD, Molnar R. Intraoperative patient-controlled analgesia: An alternative to physician administration during outpatient monitored anesthesia care. Anesth Analg 1992;75:41-4.
28. Cook LB, Lockwood GG, Moore CM, Whitwam JG. True patient-controlled sedation. Anaesthesia 1993;48:1039-44.
29. Bhattacharya S, MacLennan F, Hamilton MP, Templeton A. How effective is patient-controlled analgesia? A randomized comparison of two protocols for pain relief during oocyte recovery. Hum Reprod 1997;12:1440-2.
30. Thompson N, Murray S, MacLennan F, Ross JA, Tunstall ME, Hamilton MP, *et al.* A randomised controlled trial of intravenous versus inhalational analgesia during outpatient oocyte recovery. Anaesthesia 2000;55:770-3.
31. Lier MC, Douwenga WM, Yilmaz F, Schats R, Hompes PG, Boer C, *et al.* Patient-controlled remifentanil analgesia as alternative for pethidine with midazolam during oocyte retrieval in IVF/ICSI procedures: A randomized controlled trial. Pain Pract 2015;15:487-95.
32. Manica VS, Bader AM, Fragneto R, Gilbertson L, Datta S. Anesthesia for *in vitro* fertilization: A comparison of 1.5% and 5% spinal lidocaine for ultrasonically guided oocyte retrieval. Anesth Analg 1993;77:453-6.

33. Botta G, D'Angelo A, D'Ari G, Merlino G, Chapman M, Grudzinskas G. Epidural anesthesia in an *in vitro* fertilization and embryo transfer program. J Assist Reprod Genet 1995;12:187-90.
34. Viscomi CM, Hill K, Johnson J, Sites C. Spinal anesthesia versus intravenous sedation for transvaginal oocyte retrieval: Reproductive outcome, side-effects and recovery profiles. Int J Obstet Anesth 1997;6:49-51.
35. Guasch E, Ardoy M, Cuadrado C, González Gancedo P, González A, Gilsanz F. Comparison of 4 anesthetic techniques for *in vitro* fertilization. Rev Esp Anestesiol Reanim 2005;52:9-18.
36. Piroli A, Marci R, Marinangeli F, Paladini A, Di Emidio G, Giovanni Artini P, *et al.* Comparison of different anaesthetic methodologies for sedation during *in vitro* fertilization procedures: Effects on patient physiology and oocyte competence. Gynecol Endocrinol 2012;28:796-9.
37. Azmude A, Agha'amou S, Yousefshahi F, Berjis K, Mirmohammad'khani M, Sadaat'ahmadi F, *et al.* Pregnancy outcome using general anesthesia versus spinal anesthesia for *in vitro* fertilization. Anesth Pain Med 2013;3:239-42.
38. Aghaamoo S, Azmoodeh A, Yousefshahi F, Berjis K, Ahmady F, Qods K, *et al.* Does spinal analgesia have advantage over general anesthesia for achieving success in *in-vitro* fertilization? Oman Med J 2014;29:97-101.
39. Heo HJ, Kim YY, Lee JH, Lee HG, Baek SM, Kim KM. Comparison of chemical pregnancy rates according to the anesthetic method during ultrasound-guided transvaginal oocyte retrieval for *in vitro* fertilization: A retrospective study. Anesth Pain Med (Seoul) 2020;15:49-52.
40. 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.
41. Corson SL, Batzer FR, Gocial B, Kelly M, Gutmann JN, Go KJ, *et al.* Is paracervical block anesthesia for oocyte retrieval effective? Fertil Steril 1994;62:133-6.
42. 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.
43. Ng EH, Tang OS, Chui DK, Ho PC. A prospective, randomized, double-blind and placebo-controlled study to assess the efficacy of paracervical block in the pain relief during egg collection in IVF. Hum Reprod 1999;14:2783-7.
44. Ng EH, Tang OS, Chui DK, Ho PC. Comparison of two different doses of lignocaine used in paracervical block during oocyte collection in an IVF programme. Hum Reprod 2000;15:2148-51.
45. Ng EH, Chui DK, Tang OS, Ho PC. Paracervical block with and without conscious sedation: A comparison of the pain levels during egg collection and the postoperative side effects. Fertil Steril 2001;75:711-7.
46. Ramzy A, Hefzy OM, Rhodes CA, Sattar MM, Al-Wasseef MM, Serour G, *et al*. Ovarian sub-capsular and vaginal needle site infiltration of local anaesthetic: Evaluation of a novel method of pain relief after oocyte retrieval. Middle East Fertil Soc J 2001;6:169-74.
47. Ng EH, Miao B, Ho PC. A randomized double-blind study to compare the effectiveness of three different doses of lignocaine used in paracervical block during oocyte retrieval. J Assist Reprod Genet 2003;20:8-12.
48. Tummon I, Newton C, Lee C, Martin J. Lidocaine vaginal gel versus lidocaine paracervical block for analgesia during oocyte retrieval. Hum Reprod 2004;19:1116-20.
49. Öztürk E, Günaydin B, Karabacak O, Tuncer B, Erdem M, Erdem A, *et al*. Remifentanil infusion and paracervical block combination versus remifentanil infusion alone during *in vitro* fertilisation (IVF). Turk J Med Sci 2006;36:105-11.
50. Atashkhoii S. Conscious sedation with and without paracervical block for transvaginal ultrasonically guided oocyte collection: A comparison of the pain and sedation levels, and postoperative side effects. Iran J Reprod Med 2006;4:51-6.
51. Cerne A, Bergh C, Borg K, Ek I, Gejervall AL, Hillensjö T, *et al.* Pre-ovarian block versus paracervical block for oocyte retrieval. Hum Reprod 2006;21:2916-21.
52. Gunaydin B, Ozulgen IK, Ozturk E, Tekgul ZT, Kaya K. Remifentanil versus remifentanil with paracervical block on plasma remifentanil concentrations and pulmonary function tests for transvaginal ultrasound-guided oocyte retrieval. J Opioid Manag 2007;3:267-72.
53. Milanini MN, D'onofrio P, Melani Novelli AM, Dabizzi S, Cozzi C, Evangelisti P, *et al.* Local anesthesia versus intravenous infusion of remifentanil for assisted reproductive technologies. A retrospective study. Minerva Ginecol 2008;60:203-7.
54. Bumen S, Gunusen I, Firat V, Karaman S, Akdogan A, Goker E. A comparison of intravenous general anesthesia and paracervical block for *in vitro* fertilization: Effects on oocytes using the transvaginal technique. Turk J Med Sci 2011;41:801-8.
55. Oliveira GL Jr., Serralheiro FC, Fonseca FL, Ribeiro OD Jr., Adami F, Christofolini DM, *et al.* Randomized double-blind clinical trial comparing two anesthetic techniques for ultrasound-guided transvaginal follicular puncture. Einstein (Sao Paulo) 2016;14:305-10.
56. Rolland L, Perrin J, Villes V, Pellegrin V, Boubli L, Courbiere B. IVF oocyte retrieval: Prospective evaluation of the type of anesthesia on live birth rate, pain, and patient satisfaction. J Assist Reprod Genet 2017;34:1523-8.
57. Ma YY, Shen Y, Zhang LS. Comparison of midazolam and propofol as conscious sedation in oocyte retrieval of IVE-ET. Zhejiang Da Xue Xue Bao Yi Xue Ban 2008;37:304-7.
58. Jarahzadeh MH, Davar R, Hajiesmaeili MR, Entezari A, Musavi F. Remifentanil versus fentanyl for assisted reproductive technologies: Effect on hemodynamic recovery from anesthesia and outcome of ART cycles. Int J Fertil Steril 2011;5:86-9.
59. Coetsier T, Dhont M, De Sutter P, Merchiers E, Versichelen L, Rosseel MT. Propofol anaesthesia for ultrasound guided oocyte retrieval: Accumulation of the anaesthetic agent in follicular fluid. Hum Reprod 1992;7:1422-4.
60. Hong JY, Jee YS, Luthardt FW. Comparison of conscious sedation for oocyte retrieval between low-anxiety and high-anxiety patients. J Clin Anesth 2005;17:549-53.
61. Endler GC, Stout M, Magyar DM, Hayes MF, Moghissi KS, Sacco AG. Follicular fluid concentrations of thiopental and thiamylal during laparoscopy for oocyte retrieval. Fertil Steril 1987;48:828-33.
62. Shapira SC, Chrubasik S, Hoffmann A, Laufer N, Lewin A, Magora F. Use of alfentanil for in vitro fertilization oocyte retrieval. J Clin Anesth 1996;8:282-5.
63. De Amici D, Ceriana P, Coven G, Noli S, Cadregari F. Intravenous anesthesia during oocyte harvesting for *in vitro* fertilization. Description of a method. Minerva Anestesiol 1992;58:57-60.
64. 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.
65. 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.
66. 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.
67. Huang HW, Huang FJ, Kung FT, Tsai MY, Lin H, Chang SY, *et al.* Effects of induction anesthetic agents on outcome of assisted reproductive technology: A comparison of propofol and thiopental sodium. Chang Gung Med J 2000;23:513-9.
68. Coskun D, Gunaydin B, Tas A, Inan G, Celebi H, Kaya K. A comparison of three different target-controlled remifentanil infusion rates during target-controlled propofol infusion for oocyte retrieval. Clinics (Sao Paulo) 2011;66:811-5.
69. Sarikaya HB, Iyilikci L, Gulekli B, Posaci C, Erbil Dogan O, Ok E, *et al.* Comparison of the effects of 2 different doses of remifentanil infusion for sedation during *in-vitro* fertilization procedure. Saudi Med J 2011;32:689-94.
70. Liang FG, Shi YS, Ding H, Zhou W, Gu MN. Application of subclinical doses of pentazocine and propofol in painless vaginal egg retrieval. Nan Fang Yi Ke Da Xue Xue Bao 2011;31:373-6.
71. Goutziomitrou E, Venetis CA, Kolibianakis EM, Bosdou JK, Parlapani A, Grimbizis G, *et al.* Propofol versus thiopental sodium as anaesthetic agents for oocyte retrieval: A randomized controlled trial. Reprod Biomed Online 2015;31:752-9.
72. Elnabtity AM, Selim MF. A prospective randomized trial comparing dexmedetomidine and midazolam for conscious sedation during oocyte retrieval in an *in vitro* fertilization program. Anesth Essays Res 2017;11:34-9.
73. Morue HI, Raj-Lawrence S, Saxena S, Delbaere A, Engelman E, Barvais LA. Placebo versus low-dose ketamine infusion in addition to remifentanil target-controlled infusion for conscious sedation during oocyte retrieval: A double-blinded, randomised controlled trial. Eur J Anaesthesiol 2018;35:667-74.
74. Tola EN. The effect of anesthetic agents for oocyte pick-up on *in vitro* fertilization outcome: A retrospective study in a tertiary center. Taiwan J Obstet Gynecol 2019;58:673-9.
75. Farzi F, Mehrafza M, Mirmansouri A, Sorouri ZZ, Roushan ZA, Raoufi A, *et al.* Hemodynamic parameters and reproductive outcome after intracytoplasmic sperm injection and fresh embryo transfer in patients undergoing oocyte retrieval with general anesthesia using fentanyl, remifentanil or alfentanil – A randomized clinical trial. Taiwan J Obstet Gynecol 2019;58:536-40.
76. Matsota P, Sidiropoulou T, Vrantza T, Boutsikou M, Midvighi E, Siristatidis C. Comparison of two different sedation protocols during transvaginal oocyte retrieval: Effects on propofol consumption and IVF outcome: A prospective cohort study. J Clin Med 2021;10:963.
77. Orak Y, Tolun Fİ, Bakacak M, Yaylalı A, Kıran H, Öksüz H, *et al.* Effects of propofol versus sevoflurane on postoperative pain and neuroendocrine stress response in oocyte pickup patients. Pain Res Manag 2021;2021:5517150.
78. Saravanaperumal G, Udhayakumar P. Opioid-free TIVA improves post- operative quality of recovery (QOR) in patients undergoing oocyte retrieval. J Obstet Gynaecol India 2022;72:59-65.
79. Handa-Tsutsui F, Kodaka M. Effect of nitrous oxide on propofol requirement during target-controlled infusion for oocyte retrieval. Int J Obstet Anesth 2007;16:13-6.
80. 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.
81. Tsen LC, Schultz R, Martin R, Datta S, Bader AM. Intrathecal low-dose bupivacaine versus lidocaine for *in vitro* fertilization procedures. Reg Anesth Pain Med 2001;26:52-6.
82. 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.
83. Shao X, Qin J, Li C, Zhou L, Guo L, Lu Y, *et al.* Tetracaine combined with propofol for painless oocyte retrieval: From a single center study. Ann Palliat Med 2020;9:1606-13.
84. Ng EH, Miao B, Ho PC. Anxiolytic premedication reduces preoperative anxiety and pain during oocyte retrieval. A randomized double-blinded placebo-controlled trial. Hum Reprod 2002;17:1233-8.
85. Sacha CR, Mortimer R, Hariton E, James K, Hosseini A, Gray M, *et al.* Assessing efficacy of intravenous acetaminophen for perioperative pain control for oocyte retrieval: A randomized, double-blind, placebo-controlled trial. Fertil Steril 2022;117:133-41.
86. Seidler EA, Vaughan DA, Leung AQ, Sakkas D, Ryley DA, Penzias AS. Routine ketorolac at oocyte retrieval decreases postoperative narcotic use by more than 50. F S Rep 2021;2:156-60.
87. Humaidan P, Stener-Victorin E. Pain relief during oocyte retrieval with a new short duration electro-acupuncture technique – An alternative to conventional analgesic methods. Hum Reprod 2004;19:1367-72.
88. Gejervall AL, Stener-Victorin E, Möller A, Janson PO, Werner C, Bergh C. Electro-acupuncture versus conventional analgesia: A comparison of pain levels during oocyte aspiration and patients' experiences of well-being after surgery. Hum Reprod 2005;20:728-35.
89. Kwan I, Wang R, Pearce E, Bhattacharya S. Pain relief for women undergoing oocyte retrieval for assisted reproduction. Cochrane Database Syst Rev 2018;5:CD004829.
90. Cheung CW, Yee AW, Chan PS, Saravelos SH, Chung JP, Cheung LP, *et al.* The impact of music therapy on pain and stress reduction during oocyte retrieval – A randomized controlled trial. Reprod Biomed Online 2018;37:145-52.
91. Ockhuijsen HD, Ophorst I, Hoogen AV. The experience of Dutch women using a coping intervention for oocyte retrieval: A qualitative study. J Reprod Infertil 2020;21:207-16.
92. Ioscovich A, Eldar-Geva T, Weitman M, Altarescu G, Rivilis A, Elstein D. Anesthetic management for oocyte retrieval: An exploratory analysis comparing outcome in *in vitro* fertilization cycles with and without pre-implantation genetic diagnosis. J Hum Reprod Sci 2013;6:263-6.
93. Shaikh SI, Kumari RV, Hegade G, Marutheesh M. Perioperative considerations and management of patients receiving anticoagulants. Anesth Essays Res 2017;11:10-6.
94. Jirge PR, Patwardhan S, Jirge SN, Bhomkar DA, Chougule SM, Salpekar A, *et al.* Resuming assisted reproduction services during COVID-19 pandemic: An initial Indian experience. J Hum Reprod Sci 2020;13:323-32.
95. Humaidan P, Nelson SM, Devroey P, Coddington CC, Schwartz LB, Gordon K, *et al.* Ovarian hyperstimulation syndrome: Review and new classification criteria for reporting in clinical trials. Hum Reprod 2016;31:1997-2004.
96. Kaye A, Urman R. Obstetric Anesthesia Practice. New York: Oxford University Press; 2021. p. 409.
97. Greenberger C, Matot I, Artsi H, Samara N, Azem F. High level of satisfaction among women who underwent oocyte retrieval without anesthesia. Fertil Steril 2020;114:354-60.
98. Gilboa D, Seidman L, Kimiagarov P, Noni A, Doron R, Seidman DS. Why do women choose to undergo oocyte aspiration without sedation or analgesia? Reprod Fertil 2021;2:89-94.