Office Based Anesthesia Guidelines: Policy Recommendations for Oocyte Retrieval

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Office based anesthesia is a cornerstone of efficient, cost effective care for generally low risk procedures. Primarily, fertility care is often done within the office environment due to the fairly low risk environment, combined with the cost saving measures versus standard operating room (OR) utilization (Osman & Shapiro, 2019). Office based anesthesia is defined by the American Society of Anesthesiologists (ASA) as "the performance of any surgical or other invasive procedure requiring anesthesia, analgesia, or sedation, including cryosurgery, laser surgery and the use of lasers that penetrate the skin, which results in patient stay of less than 24 consecutive hours and is performed by a licensee in a location other than a hospital or ambulatory surgical center" (2019). Office environments present a cost-effective and arguably more comfortable environment for practitioners and patients, with some studies finding a 40% reduction in cost (Chambers et al., 2020). This cost effectiveness is one of the primary reasons that, as of 2019, office-based procedures account for 15-20% of all out of hospital procedures (Osman & Shapiro, 2019). Of these office-based procedures, oocyte retrievals are of particular interest.

Oocyte retrievals are commonly done within an office-based environment and present particular challenges to anesthesia providers, patients and physicians alike. These retrievals are often costly for the patient, with insurance coverage being minimal to absent, they require mood-and-physiology altering hormone administration, and can be quite uncomfortable, both physically and psychologically. Retrievals can be unsuccessful despite best efforts, and this prospect can loom over patients who have likely experienced a history of difficulty and frustration conceiving. Oocyte retrieval can be quite painful and thus traumatic for patients who do not receive sufficient and holistic anesthetic care. The retrieval environment requires

confidence from both parties to achieve optimal retrieval of oocytes and provide optimal patient outcomes. As such, this proposal is intended to identify challenges surrounding oocyte retrieval and provide optimal clinical guidelines for anesthesia providers.

Background

A meta-analysis supported by the World Health Organization found that, "pooled estimates of lifetime and period prevalence of 12-month infertility were 17.5% and 12.6%, respectively" (Cox et al., 2021, pg. 1). In 2015, assisted reproductive technology (ART) helped conceive approximately 2% of all births, including 17% of all multi-birth infants (Sunderam et al., 2018). Anesthetic demand in ART can only be expected to increase, not only because of a gradually increasing morbidity-burden in reproductive-age females, but also due to a generational trend of intentionally delaying childbearing until later in life, particularly among professional couples (Lampic et al., 2006). In 2020, one fifth of U.S. pregnancies involved mothers of advanced maternal age (35 years or older), which raises the risk of adverse maternal, fetal, and neonatal outcomes, in addition to making conception more difficult (Osterman et al., 2021). After age 35, the gradual decline in female fertility becomes exponential, and the probability of pregnancy in any given cycle is only 5% by age 40 (Owen, 2024). There is also a significant correlation between chronic disease and infertility (Murugappan et al., 2019). Among reproductive-age females of the western world, those in the United States have the highest incidence of chronic disease, including obesity, diabetes, hypertension, cancer, heart disease, chronic lower respiratory tract illness, chronic liver disease and psychiatric comorbidity, with prevalence increasing (Hayes et al., 2020). Also of note, despite paying the highest out-of-pocket costs for medical expenses of all developed nations, U.S. women also have the highest maternal

mortality rate (Gunja et al., 2022). Despite this trend in conception patterns, there remains no established best-practice anesthetic recommendations for such critical biomedical services.

Office-based surgery is desirable for both patient and provider by improving access and convenience with presumably lesser cost and shorter time-commitment. Office-based settings are more cost-effective than alternative practice settings. Mean total, allowed, and scaled charges for office-based procedures are significantly lower than the same procedure performed in an operating room (OR) (Prickett et al., 2012). Office-based procedures are reimbursed at the same or an even higher rate than surgeries performed in the OR (Prickett et al., 2012). Importantly, office-based practices are not subject to the same local, state, and federal regulations as hospitals or ambulatory surgical centers, providing further financial and regulatory incentives (Urman et al., 2012). Unfortunately, the rates of perioperative complications following Office-Based Anesthesia (OBA) remain ten times the rates after ambulatory surgery (Beard et al., 2023).

It is recognized that office-based settings often lack the regulation and oversight afforded to acute care hospitals and ambulatory surgical centers leading to limited oversight and violations of minimal safety-&-practice guidelines. Office-based settings are especially prone to practice drift, where providers deliver care above their scope of practice. Another regulatory issue is that approximately half of states do not require accreditation of office-based practices (Urman et al., 2012). The delivery of a substandard anesthetic due to suboptimal practice conditions can be in part due to reduced anesthetic standards, a lack of supplies, or the absence of licensed anesthetic professionals. States generally delegate the construction of rules for office-based surgery to their associated medical boards, which near-universally reference practice recommendations put forth by the ASA.

Regarding relevant standards for performing office-based anesthesia, the ASA states that:

> Office-based facilities should have personnel, equipment, and drugs to initiate treatment of any crisis situation including unanticipated difficult airway, anaphylaxis, local anesthetic systemic toxicity, malignant hyperthermia [MH]), or major cardiovascular events including cardiac arrest. The facility should stock difficult airway tools (video-laryngoscopes), defibrillators, emergency drugs for advanced cardiac life support (ACLS), and 20% lipid emulsion to treat systemic toxicity of local anesthetics. (Shapiro et al., 2014)

Standards for providing office-based anesthesia should be equivalent to those used in hospitals and ambulatory surgery settings, including possession of a designated area for post-procedure recovery. Office-based anesthesia environments should also use standard ASA monitoring modalities and a minimum of two regulated oxygen-sources (one compressed source being equivalent to a full E-cylinder). These office-based settings should also have the ability to provide positive pressure ventilation with an FiO2 of at least 90%, a reliable source of suction, and a lockable anesthesia cart containing supplies for endotracheal intubation and laryngeal mask airways. There should also be standard emergency medications available, including pharmacology for managing hemodynamic instability (American Society of Anesthesiologists, 2019).

Critically important to office-based settings, anesthesia providers must possess the competence and means to convert to or rescue from a deeper than intended plane of anesthesia—a requirement which may not be met by RN-driven sedation protocols. Anesthesia providers must also recognize that hypoxia secondary to respiratory depression is the most common mechanism of patient injury in completed court claims otherwise known as “closed claims data” for office-based anesthesia (Yeh et al., 2020). Unintentionally entering a deeper anesthetic level

cannot justify inadequate resource allocation for managing patients having entered such deeper planes. The ability to rescue patients from respiratory or hemodynamic collapse is a standard of care for anesthesia providers (ASA, 2020). Protocols are necessary for the safe and timely transfer of patients to an alternate care facility, such as a hospital with fully equipped operating room, in the event that extended or emergency services are needed to protect the health or well-being of the patient (ASA, 2019).

The CRNAs at one local institution providing fertility services have always experienced intentional restriction of essential pharmacology (propofol access) mandated by their anesthesia department management. This was established based on a premise that access to propofol should not be necessary for proceeding through the expected conditions of the low-acuity office-based anesthesia setting (i.e., conscious sedation with a spontaneously breathing patient and patent airway). For this reason, alfentanil was essential in the anesthetic planning for oocyte retrieval procedures however after its discontinuation, there are few options available after the discontinuation of alfentanil without the ability to use propofol.. Unfortunately, this perspective discounts the reality that most emergencies are inherently deviations from routine expectations and that swift conversion to general anesthesia may suddenly become necessary. This rule of propofol availability would not be endorsed by the ASA, American Association of Nurse Anesthetists (AANA), or Oregon Medical Board (OMB). Due to the limited oversight and guidance available for office-based settings, changes like these remain unchallenged.

Regulations for office-based anesthesia (OBA) can vary by state. The most recent permanent administrative order set forth by the Oregon Medical Board (OMB) are as follows (2023): Office based anesthetics are classified as level I (not requiring anesthesia services), level II, which are surgical procedures performed under *moderate* sedation and analgesia, or Level III,

which are major surgical procedures that require either *deep* sedation & analgesia, general anesthesia, or regional nerve blockade, and may require the the support of bodily functions by an anesthetist.

Other regulations restrict the fertility specialist from administering anesthesia other than additional local anesthesia, and also prevents them from being responsible for monitoring or managing anesthesia during the procedure (Oregon Medical Board, 2023). Prohibited from being performed in an office-setting are procedures that may result in blood loss of more than 4% of the estimated blood volume (assuming normal Hgb), procedures requiring either intracranial, intrathoracic, or abdominal cavity entry, and any joint replacement operations (Oregon Medical Board, 2023). Lastly, level II or III procedures on patients with an ASA Status IV or higher cannot be performed by CRNAs (Oregon Medical Board, 2023). In addition to the requirements of any legally practicing CRNA, it is necessary for the provider to receive continuing education in the field for which services are being provided (Oregon Medical Board, 2023).

Per the OMB (2023), the CRNA providing sedation or anesthesia is individually responsible for the verification or determination of the client's ASA status, accompanied with documentation reflecting the assessment and conclusion supporting the ASA classification. Likewise, it is the CRNA's responsibility to ultimately ensure that the patient satisfies the criteria for OBA. Alongside the American Association of Nurse Anesthetists (AANA) The provider is to verify that all monitors and equipment are maintained, functional, compliant with current medical standards, and accompanied by alternative power-sources. CRNAs are to ensure that standard ASA monitors are used throughout the procedure (heart rate, capnography, blood pressure, respirations, and pulse oximetry, at minimum) and for an appropriate recovery period thereafter, not unlike the delivery of any other anesthetic. The CRNA should also ensure that

there are sufficient personnel and equipment to safely complete the procedure, as well as appropriately plan for and treat any possible complications. This may include having emergency equipment immediately available, access to emergency-pharmacology and various airway-management supplies, as well as advanced cardiopulmonary resuscitation capabilities. CRNAs are responsible for safely managing the anesthetic recovery and discharge of patients. Lastly, the CRNA should confirm agreements and systems for transportation of a patient to a higher level of care if necessary. (AANA, 2024).

The AANA dictates that if triggering agents are used in a facility (volatile, halogenated anesthetics such as desflurane or sevoflurane and succinylcholine), then a cost-prohibitive supply of dantrolene must be available to treat a potential malignant hyperthermia (MH) crisis (Beard et al., 2023). As of 2018, one 250mg vial of Ryanodex (Dantrolene Sodium) IV-powder costs approximately $3,450. The Malignant Hyperthermia Association of the United States (MHAUS) considers an appropriate facility reserve to be three vials (Ho et al., 2018). This high cost discourages most OBA settings from stocking volatile anesthetics or succinylcholine (Beard et al., 2023)l. Lastly, the AANA states that patients with poorly controlled diabetes, a history of substance use disorder, seizure disorders, MH-susceptibility, potentially complex airways, a nothing by mouth (NPO) period of less than eight hours, no home-escort, previous adverse anesthetic complications, or risk of aspiration unsuitable for meeting OBA candidate criteria (Beard et al., 2023).

The majority of states, including Oregon and Washington, do not require insurance companies to provide infertility benefits. Despite being necessary for conception in many cases, fertility treatment is considered medically unnecessary by insurers (Peipert et al., 2022). Therefore, most patients presenting for oocyte retrieval have spent significant out-of-pocket costs

to obtain a potentially hazardous and painful procedure. The average cost for a single IVF cycle ranges between $24,373 and $38,015 (Katz et al., 2011). This amount can fluctuate depending on whether or not gonadotrophic pharmacotherapy is billed separately or if additional genetic testing is requested. This cost does not account for the potential failure of an IVF cycle or consider that total cost per successful outcome increases with the patient's age (Chambers et al., 2006). In 2009, the average successful pregnancy cost utilizing IVF was between $60,000 - $70,000 over an 18-month period, not including indirect costs associated with hormone therapy, consistent visits to both specialists and primary care providers, etc (Katz et al., 2011). The financial sacrifice, the emotional distress of attempting to conceive, as well as the side effects of gonadotropin agonist/antagonist pulse treatment may create a high-stress environment for both the patients and anesthesia providers. Noble expectations of comfort may challenge the pharmacological arsenal afforded to the anesthetist, particularly without concurrently inducing undesirable effects (e.g., postoperative nausea and vomiting (PONV), apnea) or prolonging recovery from anesthesia.

Current events pertaining to opioid diversion and patient harm have been propagated by social media and have promoted public uncertainty in the quality of anesthetic care provided to patients for this specific procedure (Burton et al., 2023). This media sensationalism was likely seeking promotion of public distrust in healthcare, leading to increased suspicion of healthcare authorities.

Unfortunately, there is a basis for the distrust in anesthesia providers and diversion of controlled substances. The incidence of substance use disorders (SUD) among faculty and resident physicians in anesthesiology is between 1-2%, and appears to be increasing (Fitzsimons, 2023). In addition to the safety concerns regarding practitioner impairment, the incidence of

relapse among affected providers is 43%. Death is often the presenting sign of misuse – the mortality rate for SUD in anesthesia professionals has even been estimated at 20% (Fitzsimons, 2023). A Brazilian study reported that most anesthesiologists (over 80%) have known of at least one anesthesia provider with SUD, and nearly a quarter of those surveyed admitted to personal use at some point in their lives (Sousa et al., 2021). Bell et al. (1999) noted that up to 10% of nurse anesthetists reported misusing an anesthetic agent at some point in their career. Nonetheless, there is no association between anesthetic duty and IVF-procedures as reports of intentional anesthetic harm remain scarce, and absence of amnesia 0.1-0.2% (Tasbihgou, 2018).

Lastly, patients presenting for trans-vaginal oocyte retrieval (TORP) may have higher sedation requirements in part due to the required non-physiological hormone augmentation. When discussing this with participants in the survey, it was repeated by all three practitioners that the points for which anesthesia is utilized is once the patient lies down on the procedure table and throughout the procedure until the end. The anesthetic is followed by analgesia provided in order to blunt response to the needle penetrating the follicles. The challenge however is the procedure does not need long acting opioids which is why fentanyl is commonly used (Malvasi & Baldini, 2019).

Specific research on this topic is scarce, yet anesthetic needs may vary depending on the phases of the menstrual cycle (Guasch et al., 2019), with estrogen levels being highest during the follicular phase (Kurdy & Ramaswamy, 2019). The required propofol dose in patients undergoing TORP has been shown to directly correlate with serum estradiol–but not progesterone–concentrations (Guasch et al., 2019). Basaran et al. (2019) similarly found a positive correlation between serum estrogen concentration and propofol dose required for loss of consciousness during retrieval. In the adult endoscopy setting, higher conscious sedation

requirements are associated with younger age, outpatient opioid or benzodiazepine use, as well as duration and complexity of procedure (McCain et al., 2020). No firm association between gender and anesthetic requirements exists, although red-haired females in one study required higher anesthetic doses (Nagelhout & Elisha, 2018). Additionally, a recent retrospective cohort study found that female gender, younger age, use of sedation adjuncts, non-smoking status, outpatient benzodiazepine and/or opioid use, or procedural difficulty encountered to be significantly associated with a higher likelihood of failed conscious sedation during endoscopic procedures (Cassell et al., 2020).

Purpose

Oocyte retrievals are complex procedures that have an everlasting effect on the lives of women and the providers that care for them. For anesthesia providers, it is within their interest to advocate for patients within their scope to provide optimal procedural outcomes. The women who invest their money, time and lives to achieve parenthood deserve an optimal anesthetic environment to ensure their fertility success. The purpose of this project is to review the available literature on regional anesthetic techniques for oocyte retrieval and compare findings with national consensus statements and guidelines from certifying bodies on optimal anesthetic technique. This project will allow the development of optimal anesthetic techniques, refine patient monitoring recommendations, and describe environmental considerations for oocyte retrieval in office-based settings.

The purpose of this project is to synthesize the best available evidence with policies, practices, and standards of care in the Pacific Northwest in order to construct veritable recommendations for anesthetic care delivery with IVF and other assistive-reproductive procedures. These recommendations will act as scaffolding for any group offering reproductive

assistive technology or seeking to establish a practice within this specialty. Local approaches to anesthesia delivery for TORP will be gathered through focused, semi-structured interviews with CRNAs providing anesthesia for these procedures. Policymakers addressing anesthetic standards at two assisted-reproductive facilities will also be interviewed.

Methods

For this project, a Data-Driven Policy framework was chosen to facilitate recommendations for policy (J, J., D, L., & L, B, 2016). This framework utilizes multiple stages of development and allows for the use of both qualitative and quantitative data to guide policy recommendations. Utilizing this model; an extensive analysis of literature regarding anesthetic technique for oocyte retrieval was then followed by an analysis of current policy from federal, state and organizational regarding office based anesthesia and semi-structured interviews with Nurse Anesthetists within the Portland, Oregon area. These results are then compared with current literature to provide recommendations.

These semi-structured interviews contain 13 semi-structured questions performed either in person or via video conferencing. The participants were acquired through cold emails to facilities in the Pacific Northwest along with personal requests. Participants verbally consented to the survey. The questions for the survey inquired about the presence of safety equipment, anesthetic techniques used, patient outcomes, and failure rates due to anesthetic technique and patient ASA levels. No specific patient data was gathered. Data were compared with a qualitative analysis of literature associated with anesthetic recommendations for oocyte retrieval.

Results

A total of three surveys were conducted with regional Nurse Anesthetists. The survey results were combined with 13 articles related to anesthetic technique of oocyte retrieval. The most

common anesthetic agent from those surveyed was propofol, followed by midazolam. None of the anesthesia providers or articles utilized midazolam as a primary agent; rather, it is used adjunctively for both anterograde amnesia and anxiolysis. Fentanyl was the most frequently used opioid, administered shortly prior to tissue puncture as well as for breakthrough pain, although one respondent also routinely pre-medicated with oral hydromorphone before procedure start. In regards to antiemetic agents, 100% of the respondents utilized propofol and ondansetron as primary antiemetic agents (note that this does not include the outlier institution that did not grant its anesthesia providers access to propofol for TORP, whose IVF-program is now defunct). However, data on antiemetic agents was sparse with 50% of articles not recommending or specifying any antiemetic agent over another.

In regards to perioperative concerns, 100% of the survey participants reported a goal of moderate-deep sedation level which correlates with the literature recommendations of moderate-deep levels of sedation for this procedure. None of the participants had particular knowledge of state or federal guidelines for office based anesthesia; however, very few procedural failures and no adverse events occurred within the last 5 years per each participant. Then when asked about patient selection, 2/3 participants did not have absolute contraindications for office based oocyte retrieval. On average, most patients were ASA 1-2. One participant acknowledged within their practice that patients in ASA 4 levels are indefinitely deferred until health status improved, per policy. .

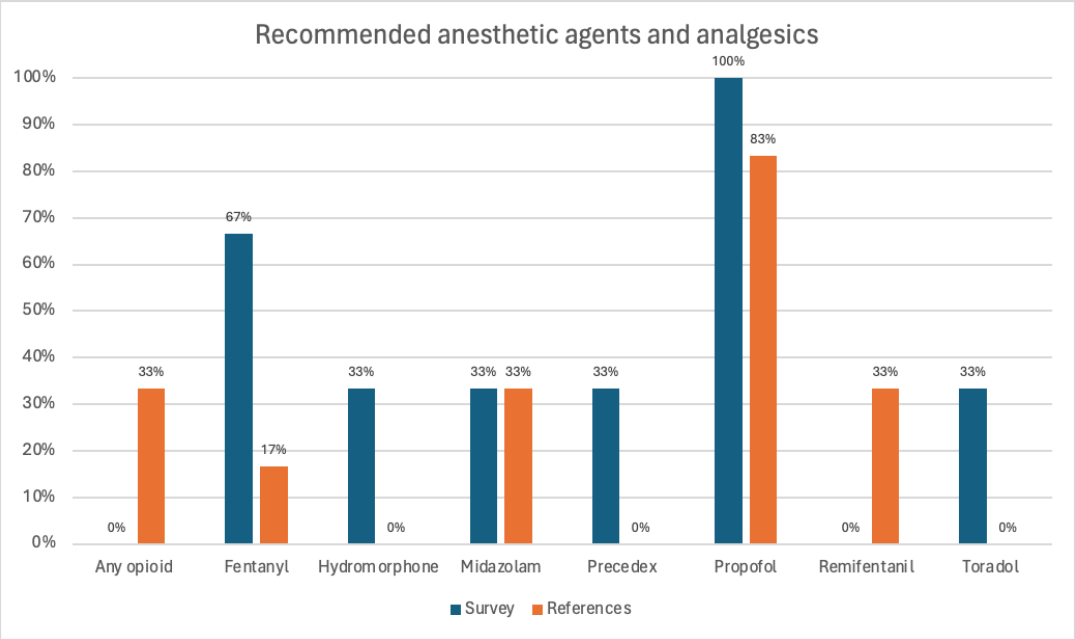

Figure A

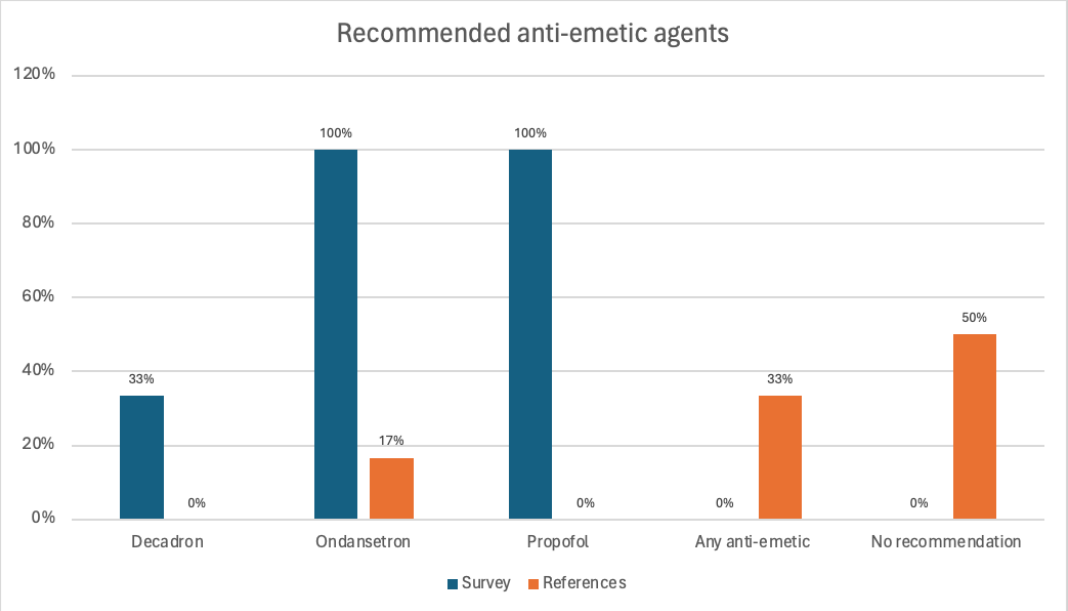

Figure B

Figure C

Discussion

Ideal anesthetic characteristics for use in office-based settings include short-acting, predictable pharmacokinetics, minimal postoperative nausea and vomiting (PONV), a high therapeutic index and cost-efficacy (Shapiro et al., 2014). This optimistic ideal remains elusive, not only because standardization in anesthetic delivery is absent, but also because no anesthetic method has demonstrated markedly superior effectiveness over another. For this reason, significant variations in technique exist, potentially resulting in patient expectations that are incongruent with national recommendations for practice or consensus statements. Additionally, substantial deviation in anesthetic technique introduces multiple confounding variables such as quantity of retrieved oocytes, rate of successful fertilization, successful pregnancy outcomes, or patient satisfaction levels. For Transvaginal Oocyte Retrieval Procedures (TORP), Guasch (2019) concludes:

> There is no strong evidence to recommend the avoidance of any technique or drug for TORP, including nitrous oxide or halogenated agents. Women should be offered any available technique. The evidence available up to date is not convincing enough to recommend avoiding any anesthetic technique in terms of pregnancy and birth rates. (p. 285)

Contrary to inconsistent anesthesia practices, TORP procedural goals remain mostly uniform. Conscious sedation is almost universally sought so that "patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained" (Malvasi & Baldini, 2019). Indeed, ninety five percent of IVF facilities surveyed report using conscious sedation (Ditkoff et al., 1997). Circeo et al. (2011), using the bispectral index monitor (BIS) to measure the sedation level of patients undergoing TORP, found that patients' BIS scores–a single number derived from a conglomerate, algorithmic calculation using EEG power and frequency of the frontal lobes, or "bispectral analysis"–generally lie between 47 and 53, which more so correlates with a state of general anesthesia and little to no probability of awareness or consciousness. Indeed, the target range for general anesthesia is a BIS value of 40 to 60 (Nagelhout & Elisha, 2018). It is likely that most facilities underestimate the level of sedation provided, and that many purported moderate-deep sedation cases readily, if intermittently, cross the threshold into general anesthesia. Conscious sedation is typically only a transient state existing at the beginning of the procedure, with deep sedation or general anesthesia being entered after the first five minutes (Circeo et al., 2011).

Many varied anesthetic regimens have been used and are often described as a balanced combination of propofol, midazolam and fentanyl (Malvasi & Baldini, 2019). One to four

milligrams of midazolam is initially administered for amnesia and anxiolysis, followed by intermittent boluses of propofol (10-20mg) with or without preemptive intravenous lidocaine (1 mg/kg) until the desired level of sedation is reached. This may also include preemptive fentanyl boluses (25-50 mcg) for a cumulative dose reaching 50-100 mcg. Alternatively, a continuous infusion of propofol is used at 80-150 mcg/kg/min, with awakening usually occurring within 10-15 minutes following infusion-cessation, or within 8 to 10 minutes post-bolus (Cascella et al., 2020). Interestingly, female patients wake up significantly faster from propofol anesthesia (5.6 minutes versus 8.2 minutes), with female plasma concentrations of propofol declining much more rapidly (Hoymork & Raeder, 2005).

Psychological stress is known to impair fertility, with elevated norepinephrine and cortisol levels associated with loss of pregnancy after TORP (Aimagambetova et al., 2020). Reproductive uncertainty, the anticipation of procedural pain, and feelings of personal vulnerability may promote intense anxiety and psychological distress within this patient population (Klonoff-Cohen et al., 2001). Anxiolysis and anterograde amnesia offered by midazolam is often appropriate in this context, with pre-treatment even being associated with lower oxidative stress, higher glutathione (antioxidant) concentrations, and lower catalase (pro-oxidant) activity in follicular fluid (Pešić et al., 2021).

Nearly all opioids, particularly of the phenylpiperidine class, are considered safe for use in fertility settings, with fentanyl & alfentanil having the least penetration into follicular fluid (Kheterpal et al., 2022). However, multiple studies have shown alfentanil to be associated with higher rates of successful pregnancy compared to fentanyl (Kheterpal et al., 2022). Unfortunately, the sole manufacturer of alfentanil, Akorn Pharmaceuticals, filed for bankruptcy in early 2023. With the loss of Alfentanil availability, the ultra-rapid pharmacokinetics of

remifentanil are appealing considering the transient but intense nature of stimulating oocyte pickup. Described as a metabolic "soft" drug, the onset and peak of remifentanil is within one minute of administration and facilitates precision analgesia concurrent with vaginal puncture and oocyte penetration (Malvasi & Baldini, 2019). Sufficient anesthesia can be attained within 30-60 seconds of a remifentanil loading dose of 0.5-1 mcg/kg, or an infusion may be started at 0.05-0.2 mcg/kg/min (Abbate et al., 2022). Organ-independent metabolism via ester hydrolysis and a constant context-sensitive half time (approximately three to four minutes) ensure a prompt and predictable offset of pharmacodynamic effect (Egan, 1995).

Patient recovery and discharge are significantly faster using remifentanil rather than alfentanil (Lin et al., 2022). Jarahzadeh et al. (2011) found remifentanil superior to fentanyl for a MAC-technique for oocyte retrieval, with higher likelihood of successful pregnancy, greater patient satisfaction, as well as faster recovery from anesthesia. Although the rapidity of remifentanil allows quick recovery without residual or recurrent narcotization (i.e. undesirable oversedation, lingering PONV, constipation, and delayed-onset respiratory depression secondary to prolonged opioid effect)–ideal for an outpatient procedure– these same properties provide little to no postoperative analgesia (Hong et al., 2007). This issue may necessitate additional post-procedural analgesia. Additionally, remifentanil induced hyperalgesia (RIH) has been described where postoperative opiate consumption and pain scores are increased by intraoperative administration of remifentanil (Fletcher & Martinez, 2014; Santonocito et al., 2018). Cumulative opioid doses used in TORP are relatively low, and mū-receptor desensitization is a time and dose dependent process, so the brief duration of the TORP procedure makes RIH unlikely in reproductive anesthesia. Despite the generally favorable results described in the literature using remifentanil for TORP, interviewees of this study expressed

institutional reluctance to use remifentanil mostly due to unfamiliarity with the medication as well as a potentially prohibitive cost to the facilities. When considering the cost savings in terms of shortened recovery and procedural times, reduction in other drug doses (i.e., propofol), and fewer unwanted effects (respiratory depression, drowsiness, cutaneous intolerance, nausea, light anesthesia incidence), the cost effectiveness of remifentanil compared to fentanyl is still favorable in adult surgery (Liu et al., 2018).

One survey respondent routinely administered ketorolac for adjunctive analgesia after TORP. Cyclooxygenase-2 inhibition has been associated with a reversible luteinized unruptured follicle syndrome, characterized by clinical signs of ovulation but without follicle rupture or release of ovum (Stone et al., 2002), also known as functional anovulation. Another concern with non-steroidal anti-inflammatory medication use is negation of the ovulatory response to a Luteinizing-Hormone (LH) trigger, which is prostaglandin dependent (Seidler et al., 2021). Despite this, multiple studies have demonstrated that administration of up to 30 milligrams of ketorolac has no demonstrable negative impact on IVF pregnancy outcomes (Mesen et al., 2013; Mesen et al., 2011; Walter, 2021). Ketorolac more than halves post-procedural opioid consumption and significantly reduces pain scores without instigating bleeding, so it may be useful in TORP recovery (Seidler et al., 2021). The analgesic ceiling dose of ketorolac may be as low as 10-15mg, although 30mg may offer additional systemic and local anti-inflammation (Yurashevich et al., 2020). Premedication with immediate release oral hydromorphone was highly effective for one respondent, allowing a reduction in intraoperative propofol and additional IV-opioid requirements. The immediate-release formulation has an onset of 15-30 minutes, peaking at 30-60 minutes and lasting three to four hours (Murray & Hagen, 2005).

Analgesia was thus provided throughout and for hours after the procedure, with peak effect approximating the most stimulating periods.

The kinetic and temporal challenges of "twilight anesthesia" lie in anticipating and preemptively responding to episodes of increased procedural stimulation which beckon transient deepening of the anesthetic plane, preferably while maintaining spontaneous ventilation and avoiding a prolonged anesthetic emergence from a relatively quick procedure. The most stimulating and uncomfortable moments of the procedure—necessitating maximum analgesia and anesthetic depth—include puncture of vaginal tissue and the ovarian capsule, which generally occurs multiple times bilaterally to maximize oocyte yield (Khetarpal et al., 2022). Direct, closed-loop two-way communication between the fertility specialist and anesthesia provider is essential at these critical moments. Most of those interviewed for this study utilized a pulse-dose of propofol (~0.5-1 mg/kg) 30-45 seconds prior to tissue puncture with or without supplemental opioid (~1 mcg/kg fentanyl). Use of a reduced needle-in-needle (20/17 gauge) results in less pain and lower analgesic necessity compared to the standard 16 gauge needle (Buisman et al., 2021), though this is not under the the jurisdiction of the anesthetist. Although the majority of women report mild or even no pain, approximately seven percent of women recall oocyte retrieval as being very or extremely painful (Frederikson et al., 2016). Predictors of higher pain intensity include previous unpleasant gynecological experiences, presence of side-effects from hormone therapy, high pre-procedure anxiety, longer procedure duration and patients' external locus of control (Frederikson et al., 2016).

With regards to the desired anesthetic depth for oocyte retrieval, survey results correlate broadly with the literature that the ideal anesthetic includes propofol as a primary anesthetic agent due to its fast onset, short half life, and intrinsic antiemetic properties. The survey results

also correlate with the limited antiemetic agent research which shows broad use of ondansetron for antiemetic prophylaxis. Postoperative nausea and vomiting (PONV) is quite common after TORP despite the avoidance of typical emetogenic agents (e.g., no volatile anesthetics) and is directly related to peak estradiol concentrations (Coburn et al., 1993). Metoclopramide may negatively impact fertility via disinhibition of prolactin secretion through D_2-antagonism, while 5-HT_3 blockade with ondansetron does not result in hyperprolactinemia and has no effect on IVF pregnancy outcomes (Mesen et al., 2011).

Propofol is an anesthetic of choice for oocyte-retrieval under sedation due to its favorable pharmacokinetics, proven safety, reliability and antiemetic properties. In TORP, however, propofol readily accumulates in follicular fluid and has been shown to deleteriously impact mitotic cleavage events (cleavage being the process within multicellular organisms wherein parent-egg cytoplasm divides into smaller, nucleated daughter cells). It also reduces sperm fusion with oocytes and prevents the formation of polar-bodies during meiosis (Haikin Herzberger et al., 2023). These reproductive and genetic disruptions are likely related to disturbances of the oocyte plasma membrane. Propofol concentrations recovered in oocytes have been shown to be directly proportional to the cumulative dose administered (Haikin Herzberger et al., 2023). A retrospective cohort study in humans determined that, when compared with no anesthesia, propofol administration for oocyte retrieval was associated with lower fertilization rates, fewer pregnancies resulting in delivery, and a higher incidence of spontaneous abortion (Haikin Herzberger et al., 2023). In a rat-model, Budak et al. (2021) also found that embryo quantity, quality and net pup-count decreased as cumulative propofol dosage increased, whereas no such negative association was found with the use of dexmedetomidine in this study. It has also been suggested that hemodynamic disturbances commonly associated with propofol administration

may reduce perfusion pressure to both myometrium and follicle, lowering reproductive viability via ischemia and tissue hypoxia, as well as causing oxygen desaturation events related to propofol-induced respiratory depression. For example, it is well known that propofol produces cardiac depression through systemic vasodilation, reduction in sympathetic tone, obliteration of the baroreceptor reflex and some degree of negative inotropy, with most hypotensive events occurring within the first ten minutes after induction (Nagelhout & Elisha, 2018). Likewise, propofol produces respiratory depression via desensitization of the central chemoreceptors to carbon dioxide tension, typically reducing tidal volume more so than respiratory rate, and frequently producing apnea with initial administration (Nagelhout & Elisha, 2018). These desaturation events can be particularly harmful to oocytes whose rate of oxygen consumption is increased by the processes of fertilization and cell multiplication (Tejera et al., 2011).

Nonetheless, the ubiquity of propofol amongst the anesthesia providers surveyed suggests that the reproductive impact of this medication may not be as clinically significant as the research implies. This discrepancy might be related to the brief duration of the TORP procedure, which could limit transfer and equilibration of lipophilic propofol between plasma and oocyte. It is also possible that data obtained from rats receiving supraphysiological doses of propofol is not transferable to human populations. An innovative solution to the propofol problem was demonstrated by Shao et al. (2019), who combined tetracaine with propofol for TORP. The addition of a local anesthetic allowed for a reduction in IV propofol dose alongside highly efficacious analgesia (described by the authors as “painless oocyte retrieval” [p. 1606]), increased operative satisfaction for both patient and provider, and improved reproductive prognosis. Other adjuncts such as remifentanil are similarly hypnotic sparing (Patel & Spencer, 1996). For example, a remifentanil infusion of 0.15mcg/kg/min results in a 66% reduction in

propofol dose required to produce hypnosis and inhibit movement to surgical stimulus, a synergistic interaction (Kerns et al., 2004; Mertens et al., 2003).

General anesthesia is associated with a transient elevation in serum prolactin & cortisol as well as suppression of progesterone production by the corpus luteum, which may have a detrimental effect on reproductive outcomes (Malvasi & Baldini, 2019). Hyperprolactinemia reduces gonadotropin-releasing hormone (GnRH) secretion with subsequent hypogonadotropic hypogonadism, anovulatory infertility, and structural endometrial changes which impede implantation (Iancu et al., 2023). Likewise, progesterone is a prerequisite for establishing a lush endometrial environment conducive to embryonic implantation. The absence of progesterone is consistently associated with spontaneous abortion (Bulletti et al., 2022). Nevertheless, due to the utero-pelvic relaxation and patient immobilization afforded by the technique, general anesthesia is also associated with a significantly greater number of collected oocytes compared to milder sedation, so the net quantity of fertilized oocytes has been shown to not differ between general and monitored anesthesia (Malvasi & Baldini, 2019). Greater oocyte yield with general anesthesia may explain why, despite our interviewees' reliance on propofol for TORP, fertilization failure was reported to be exceedingly rare, if ever encountered.

Limitations

Limitations of our study include its relatively small sample size, data being subjectively gathered, risk of voluntary-response bias, and potential coverage error, with the majority of respondents practicing locally in the PNW due to the authors' use of convenience sampling. For example, IVF-practices or anesthetic providers that did not consent to interview are not included in the sample (self-selection bias). The majority of respondents were located in the PNW due to proximity as well as some affiliations with university, which may also bias the sample if

anesthetic practices do significantly vary by region. Favorably, the anesthetic techniques and philosophies reported by our sample largely resembled those reported in the existing literature, implying generalizability of the findings. Lastly, without clarifying the concerning data (including some in-vivo studies and non-human research) proposing that propofol is abortifacient, 2,6-diisopropylphenol remains universally used by all study respondents without any noticeable detriment in fertility, and with all respondents considering it essential for their practice. Explaining this paradox beckons more prospective, quantitative data concerning the clinical effects, if any, of therapeutically-dosed propofol on human fertility. Finally, this study highlights some institutional and provider deficiencies in knowing or enforcing ASA standards for safely performing office-based anesthesia.

Conclusion

Oocyte retrieval is a highly complex procedure that presents challenges for both anesthesia provider and patient. Its success is contingent on the execution of a well-tailored anesthetic technique and the anesthesia provider's willingness to adapt to complex patient needs. More high-quality human data are essential pertaining to the ideal anesthetic technique for oocyte retrieval, however there is data suggesting that a moderate-deep anesthetic level is appropriate through enhanced patient safety and satisfaction, improved operative conditions, and successful reproductive outcomes. This anesthetic plane can be combined with numerous other adjunctive anesthetic strategies. Both the literature and provider survey results associate use of propofol with successful retrieval (Malvasi & Baldini, 2019). Combined with proper ASA recommendations for safety, including basic rescue equipment, multiple sources of oxygen, adequate suction, as well as emergency pharmacology and airway supplies (ASA, 2023), patient satisfaction, procedural success, and the prevention of adverse events is attainable.

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