Anesthesia for Assisted Reproductive Technologies

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The birth of the first in vitro fertilized baby in 1978 provoked a number of scientific, ethical, and philosophical advances and controversies with techniques known collectively as assisted reproductive technologies (ART).[1] Since 1981, when an estimated 15 to 20 babies were expected to be born worldwide with ART, the number of procedures performed has increased dramatically; in 2003, 122,872 cycles of ART led to the birth of 48,756 neonates in the United States alone (Fig. 1).[2] Reproductive biologists acknowledge that subtle differences in laboratory and clinical methods affect ART outcomes; as such, it is prudent for the anesthesiologist to facilitate ART procedures while minimizing exposure to agents with potentially adverse fertility effects.

Assisted Reproductive Techniques

Hormonal Stimulation

The goal of hormonal follicular stimulation is the production of oocytes. A typical regimen begins with a gonadotropin-releasing hormone agonist to induce pituitary suppression; this creates quiescent ovaries to prevent the development of a single dominant follicle. Follicle-stimulating hormone and human menopausal gonadotropin are then given to induce multiple (10 to 15) ovarian follicles. On occasion, an accentuated response to the medications results in a disease process called ovarian hyperstimulation syndrome (OHSS) (see below). Finally, human chorionic gonadotropin (HCG) induces oocyte maturation and movement into the follicular fluid.

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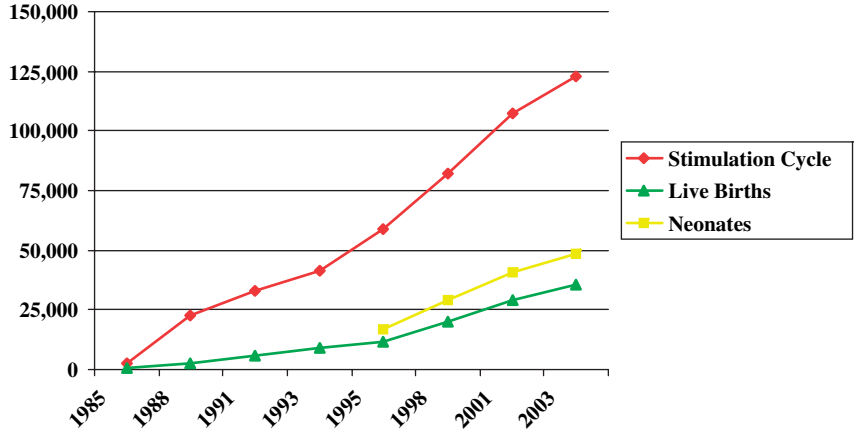

Figure 1. *Numbers for all assisted reproductive cycles initiated, deliveries, and live births reported annually to the Society for Assisted Reproductive Technology Registry.*[2]

Oocyte Retrieval

Although most commonly performed via transvaginal needle aspiration with ultrasonographic guidance (Fig. 2),[3] oocyte retrieval can be performed transabdominally or via laparoscopy, particularly when immediate tubal transfer is planned [ie, gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT)]. Oocyte retrieval is timed to occur between 34 and 36 hours after HCG administration; aspirating before and after this window misses oocytes attached to the follicular wall or those already ovulated, respectively. All visible ovarian follicles are aspirated; each follicle usually contains a single oocyte. Immediately after retrieval, oocytes are washed, incubated in culture media and examined microscopically.

In Vitro Fertilization (IVF)

Although the term *IVF* is often misused as synonymous with all aspects of ART, it applies only to the process of oocyte fertilization with spermatozoa in culture media. After a 4 to 6 hour incubation period after retrieval, oocytes are inseminated; 16 to 20 hours after insemination, the culture dishes are examined for evidence of fertilization. IVF allows the documentation of fertilization and the implementation of techniques that improve sperm motility or penetration. Male factor infertility is present in approximately 37% of the couples seeking ART procedures, and intracytoplasmic sperm injection is currently used in more than 11,000 cases annually in the United States.[2]

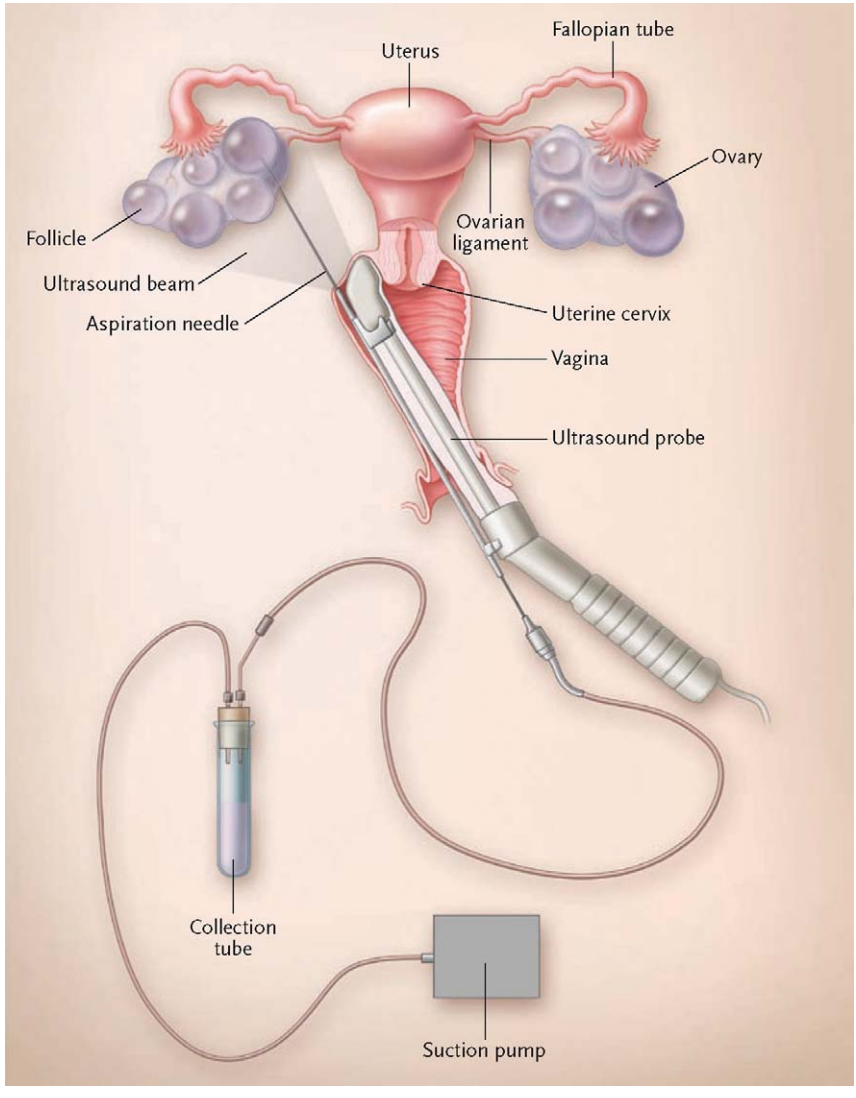

Figure 2. *Schematic representative of transvaginal oocyte retrieval. Ovarian follicles are aspirated under ultrasound guidance by means of a needle inserted through the vaginal wall. Reprinted with permission from N Engl J Med. 2006;354:4–6.*

Embryo Transfer (ET)

Embryos resulting from IVF are usually transferred 3 to 5 days after retrieval, either directly into the fallopian tubes (ie, ZIFT) or more commonly, the uterine cavity (IVF-ET). Transcervical ET can be performed without the presence of a patent fallopian tube, laparoscopy, and anesthesia, however, the probability of a successful pregnancy is

slightly less than with a ZIFT. Embryos in excess of those transferred may be frozen and stored.

Gamete Intrafallopian Transfer (GIFT)

GIFT procedures involve oocyte retrieval, inspection for quality and maturation, and placement into transfer catheter with washed sperm. The catheter is guided laparoscopically through the fimbriated end of one or both of the fallopian tubes, and the gametes injected. The catheter is inspected microscopically to verify that oocytes have not been retained. GIFT procedures allow oocyte retrieval and gamete transfer to occur during a single procedure, however, fertilization cannot be documented, requires at least one patent fallopian tube, and laparoscopic surgery.

Zygote Intrafallopian Transfer (ZIFT)

ZIFT (also known as pronuclear stage transfer) begins with oocyte retrieval, IVF, and transfer of embryos into the distal portion of a fallopian tube (as described for GIFT). ZIFT allows for the confirmation of fertilization, the avoidance of laparoscopy if fertilization does not occur, and an earlier transfer at possibly a more appropriate developmental stage. Disadvantages include the added inconvenience and cost of a 2-stage procedure, the requirement for at least one patent fallopian tube, and laparoscopic surgery.

■ Obstetric Complications

As the primary ART induced hormonal alteration, the dramatic increase in estrogen is responsible for a number of physiologic changes, including enhanced coagulation and impaired fibrinolysis.[4,5] In extremis, these alterations produce a phenomenon termed OHSS, which may result in follicular rupture and hemorrhage, pleural effusion, ascites, hemoconcentration, oliguria, and thromboembolic events.[6] Although oocyte retrieval is still performed to salvage the cycle and, more importantly, to minimize the effects of OHSS, the resulting embryos are often cryopreserved rather than transferred as the medications needed to support early embryo growth may worsen the syndrome. Rarely, an emergency laparoscopy/laparotomy may be performed for a ruptured ovarian cyst or torsion of an ovarian pedicle, or an abdominal paracentesis and/or thoracentesis may be necessary for respiratory compromise caused by massive ascites or pleural effusions.

Multiple gestation pregnancies represented 38% of the deliveries that followed ART procedures in the United States in 2003.[2] Although many infertile couples consider a twin or triplet pregnancy preferable to

a singleton pregnancy, maternal and perinatal morbidity and mortality for multiple gestation pregnancies is at least double that of singleton gestation pregnancies.[7] As such, individual programs, ART societies, and national health regulatory agencies often limit the number of oocytes/embryos transferred, and perform selective reductions if a triplet or higher order gestation occurs.

Ectopic pregnancies occur more often with ART pregnancies than with natural pregnancies, most likely due to the prevalence of tubal disease. Surprisingly, the transfer site (uterine vs. tubal) does not seem to be a predisposing factor in the development of ectopic pregnancies. Approximately, 10% of ectopic pregnancies develop in conjunction with an ongoing intrauterine pregnancy.[8] In these instances it becomes necessary to surgically remove the ectopic pregnancy during the first trimester of an ongoing intrauterine pregnancy.

Preterm delivery, low birth weight, and small-for-gestational-age babies are more common with IVF pregnancies than with natural pregnancies; however, many of these outcomes seem to be a result of infertility per se rather than ART procedures.[9]

■ Effects of Anesthesia on Reproduction

General Considerations

Ideally, anesthetic techniques and agents used for ART procedures should not interfere with oocyte fertilization or early embryo development and implantation. Although studies have observed that anesthetic agents may interfere with certain aspects of reproductive physiology in some species under certain conditions, the literature must be interpreted with caution. For example, one study concluded that general anesthesia significantly reduced oocyte cleavage rates when compared with epidural anesthesia.[10] However, a laparoscopic (instead of transvaginal) retrieval method was used in the general anesthesia group, and carbon dioxide pneumoperitoneum has been noted to significantly decrease both follicular fluid pH and oocyte fertilization rates. Another study commented on the effects of different anesthetics, yet did not disclose the actual agents administered.[11] In addition, conclusions based on animal data may not reflect the human experience due to interspecies and assay method differences.[12]

Specific anesthetic drugs must also be interpreted in context of the route of administration, dose, timing, and duration of exposure. For example, a local anesthetic agent yields different pharmacokinetic profiles when administered for paracervical, epidural, or intrathecal anesthesia. Anesthetic agents may also affect unfertilized oocytes and fertilized embryos differently; thus the same anesthetic technique and agents for a GIFT (prefertilization) procedure should not be directly

compared with that for a ZIFT (postfertilization) procedure. Finally, a significantly higher free concentration of certain agents exists during ART stimulation due to decreases in serum binding proteins.[13] Thus, when selecting an anesthetic technique and agent(s) for an ART procedure, the clinician should weigh the known benefits (eg, greater hemodynamic stability, less nausea, less psychomotor impairment) versus the hypothetical risks (eg, lower delivery rates).

Local Anesthetic Agents

In animal models, the effect of local anesthetic agents on reproductive physiology seems related to the agent, the timing, and the dose of exposure. Using mouse oocytes incubated in local anesthetics for 30 minutes, Schnell et al[14] demonstrated that lidocaine and 2-chloroprocaine adversely affected both fertilization and embryo development at concentrations of 1.0 and 0.1 μg/mL, respectively. In contrast, bupivacaine produced adverse effects only at the highest concentration studied (100 μg/mL). Similarly, Del Valle and Orihuela[15] demonstrated that after 48 hours of culture, 24% of mouse embryos exposed to lidocaine 10 μg/mL, versus none in the control group, showed evidence of degeneration. Finally, Ahuja[16] noted that hamster oocytes exposed to procaine or tetracaine demonstrated impaired zona reactions, potentially allowing additional sperm to enter and result in abnormal chromosomal numbers (polyploidy).

These in vitro findings may have limited relevance, as much lower anesthetic concentrations occur clinically and oocytes are washed and screened before fertilization and transfer. More importantly, no data from human trials condemn the use of local anesthetic agents for oocyte retrieval, GIFT, or ZIFT. Wikland et al[17] reported that the incidence of oocyte fertilization and clinical pregnancy were not decreased among women who received a modified paracervical block with lidocaine for transvaginal oocyte retrieval. Further, favorable pregnancy rates have been reported with GIFT procedures performed under epidural lidocaine anesthesia.[10]

Opioids, Benzodiazepines, and Ketamine

Fentanyl, alfentanil, remifentanil, and meperidine do not seem to interfere with either fertilization or preimplantation embryo development in animal and human trials.[18–20] When given during oocyte retrieval, fentanyl and alfenantil were detected in extremely low to nonexistent follicular fluid concentrations.[19,20] Morphine, when given in a human dose equivalent of 50 mg, allows more than one sperm to enter approximately 30% of sea urchin ooctyes.[21]

Midazolam administered systemically in preovulatory mice did not impair fertilization or embryo development in vivo or in vitro, even

when given in doses up to 500 times that used clinically.[22] When used in small bolus or infusion doses for anxiolysis and sedation for ART in humans, midazolam has not been found in follicular fluid and does not seem to cause teratogenicity.[23,24]

Ketamine in a dose of 0.75 mg/kg, administered with midazolam 0.06 mg/kg, has been noted to be an acceptable alternative to general anesthesia with isoflurane. Although the study had inadequate power, no differences in reproductive outcomes were observed.[25]

Propofol and Thiopental

The effect of propofol on reproductive outcomes is controversial; in both animal and human trials, dichotomous alterations in fertilization and early embryo development have been observed.[26–30] Most recently, pharmacokinetic and pharmacodynamic studies have demonstrated a dose and duration dependent accumulation of propofol in the follicular fluid[31,32]; however, studies correlating follicular fluid concentrations with reproductive outcome measures have observed no detrimental effects.[32,33] In addition, when general anesthesia with propofol and 50% oxygen in air was compared with paracervical blocks with mepivacaine, no differences in fertilization rates, embryo cleavage, or implantation rates were observed.[29] Moreover, a sensitive index of genotoxic effects (ie, the sister chromatid exchange assay) demonstrated no DNA damage when hamster oocytes were exposed to high concentrations of propofol (20 μg/mL).[34] Of interest, these concentrations are 40 times higher than those detected clinically in the follicular fluid of patients undergoing oocyte retrieval.[31,32] GIFT procedures conducted under propofol for induction and/or maintenance of general anesthesia have demonstrated essentially no differences in outcome when compared with other forms of anesthesia.[27] However, Vincent et al[35] demonstrated that the incidence of ongoing pregnancies was lower among women given propofol-nitrous oxide anesthesia for ZIFT when compared with a similar group given thiopental-nitrous oxide-isoflurane anesthesia. Further investigations are necessary to elucidate the full effect of propofol on reproductive outcomes.

Both thiopental and thiamylal (5 mg/kg) can be detected in follicular fluid as early as 11 minutes after administration for induction of general anesthesia in patients undergoing GIFT procedures.[36] No adverse reproductive effects have been observed with these agents, and when compared specifically to propofol (2.7 mg/kg) for GIFT procedures, no differences in clinical pregnancy rates were noted.[28]

Nitrous Oxide

Nitrous oxide reduces methionine synthetase activity, concentrations of nonmethylated folate derivatives, DNA synthesis, and mitotic spindle

function in animals and humans.[37] The overall affect on reproductive outcomes, however, seems limited. Developmental delays were observed in 2-cell mouse embryos exposed to nitrous oxide during critical embryo cleavage stages,[38] but not observed in later stages of embryo development.[39] Moreover, clinical studies of GIFT and ZIFT procedures performed with the addition of nitrous oxide find no adverse effects.[27,35,40] In a multicenter study, Beilin et al[27] observed a delivery rate of 35% and 30% with and without nitrous oxide as part of their anesthetic for a GIFT procedure.

Volatile Halogenated Agents

Volatile halogenated agents have been observed to depress DNA synthesis and mitosis in cell cultures, although the dose and timing of the exposure seems critical.[41,42] Warren et al[43] reported that 2-cell mouse embryos exposed to 3% (but not 1.5%) isoflurane for 1 hour were less likely to develop to the blastocyst stage; developmental impairment, however, was only observed when isoflurane exposure was within 4 hours of the predicted onset of cleavage.

One mechanism by which volatile halogenated agents may affect ART outcomes is through increased prolactin levels, which have been associated with diminished oocyte development and uterine receptivity. Critchlow et al[44] observed dramatic increases in plasma prolactin levels within 4 to 10 minutes of an enflurane/nitrous oxide/oxygen technique for GIFT procedures, whereas follicular fluid prolactin levels and fertilization rates were not affected. Clinical comparisons, however, suggest that specific halogenated agents can affect ART outcomes. Fishel et al[45] reported significantly lower pregnancy rates when halothane versus enflurane was administered in an effort to decrease uterine activity during ET. Similarly, Critchlow et al[44] reported lower pregnancy and delivery rates with GIFT procedures performed with halothane versus enflurane. The metabolic byproduct of sevoflurane, compound A, has been associated with genotoxic ovarian cell effects, although reproductive outcomes during ART procedures have not been assessed.[46] Caution is advised when selecting a volatile halogenated agent, especially, when contemplating the use of new agents such as sevoflurane, desflurane, and isodesox (a combination of 1% desflurane, 0.25% isoflurane, and 60% oxygen in nitrogen)[47] until further work has been done.

Antiemetic Agents

At least one study noted that droperidol and metoclopramide rapidly induce hyperprolactinemia with subsequent impairment of ovarian follicle maturation and corpus luteum function.[48] Whether such agents, particularly, when given as single doses, can affect mature

oocytes undergoing retrieval or embryos undergoing transfer is unclear; however, Forman et al[49] demonstrated that low plasma prolactin concentrations during ART procedures were associated with a higher incidence of pregnancy.

■ Anesthetic Management

Although usually healthy and in their third and fourth decade of life, individuals undergoing ART procedures are increasingly associated with significant comorbid conditions and advanced age (Table 1). As some of these conditions are associated with significant morbidity and mortality with hormonal stimulation, pregnancy, and surgical and anesthetic interventions, early multispecialty communication and collaborative decision-making is essential. A mechanism to evaluate patients with significant comorbidities, including obtaining old records, ordering tests, and initiating consultant evaluations, should be in place.

All patients should follow the fasting guidelines typically used for other patients undergoing ambulatory surgery, and for patients with risk factors for aspiration, a nonparticulate antacid and a histamine-2 receptor antagonist should be given before the procedure. On occasion, a patient may not adhere to strict fasting guidelines and although delay or cancellation of the case is an option, this decision should be made with careful analysis of the potential risks and benefits. If the window for maximal oocyte retrieval (34 to 36 h after HCG administration) is missed, spontaneous ovulation and loss of oocytes can occur, invalidating the considerable effort and expense leading to the retrieval procedure. Moreover, should follicle aspiration not be performed, the patient is at significantly increased risk for ovarian hyperstimulation syndrome, with its potential for significant morbidity. Although the mortality associated with aspiration in this patient population is difficult to quantify, it is most

Table 1. *Comorbid Conditions in Patients Seeking ART*

Reason for Seeking ART	Clinical Example
Condition prompting an attempt to preserve fertility	Condition requiring aggressive chemotherapy, radiation, or surgical intervention
	Desire to extend reproductive years
Condition associated with infertility	Obesity, endocrine and metabolic disorders
	Genetic syndromes, diseases
Condition incompatible with carrying pregnancy	Severe cardiopulmonary disorders
	Metabolic and musculoskeletal disorders

likely lower than the 0.7% mortality related to OHSS; this is particularly true if the OHSS is allowed to worsen by not retrieving the follicles.

As with other day surgery cases, the ideal anesthetic technique results in effective pain relief with minimal postoperative nausea, sedation, pain, and psychomotor impairment.

Ultrasonographic-guided Transvaginal Oocyte Retrieval

Although transvaginal oocyte retrievals can be performed under paracervical, spinal, epidural, and general anesthetic techniques, conscious sedation is the most commonly used technique.[50,51] Although usually adequate for surgical analgesia, conscious sedation often progresses to loss of consciousness (ie, general anesthesia) to prevent patient movement at critical times. The need for additional pain relief should be anticipated when the needle penetrates the cul-de-sac and later, each ovary. Of interest, one report noted a higher rate of admissions after oocyte retrieval, mostly secondary to intra-abdominal bleeding, when conscious sedation was used rather than general anesthesia.[52] Self-administered inhalational analgesia with isodesox (see above) by face mask was associated with less effective analgesia and less patient satisfaction than physician-administered intravenous analgesia.[47]

Because paracervical anesthesia incompletely blocks sensation from the vaginal and ovarian pain fibers, additional analgesia is required, even when increased doses of local anesthetic are used.[53] Epidural and spinal techniques provide excellent pain relief with minimal oocyte exposure to anesthetic agents. When compared to sedation with propofol and mask-assisted ventilation with nitrous oxide, epidural bupivacaine anesthesia resulted in fewer complications, especially nausea and emesis.[54] Spinal anesthesia may be preferable to epidural anesthesia due to the reduced anesthetic failure rate, lower systemic and follicular concentrations of anesthetic agent, and a faster recovery profile.[55] Spinal administration of 1.5% hyperbaric lidocaine (60 mg) is associated with significantly shorter recovery times than spinal administration of 5% hyperbaric lidocaine in patients undergoing ART procedures.[56] The addition of intrathecal fentanyl (10 μg) to lidocaine 45 mg improves postoperative analgesia for the first 24 hours, with no increase in time to urination, ambulation, and discharge, when compared with lidocaine alone.[57] Low-dose spinal bupivacaine has been evaluated for use in these patients, however, the prolonged time to urination and discharge may prevent it from becoming a commonly used ambulatory alternative.[58]

General anesthesia can be provided by total intravenous anesthesia using propofol (titrated) and fentanyl (50 to 100 μg), with midazolam (1 to 2 mg) as an optional premedicant. Using this option, most patients

can be managed with spontaneous ventilation via a simple oxygen mask and the use of carbon dioxide analysis.[24] Anesthetics managed in this fashion have higher patient acceptance than conscious sedation, due to improved pain relief and less awareness during the surgical procedure.[24] Alternatively, general anesthesia with intubation and maintenance with volatile halogenated agents has been used successfully; however, higher rates of nausea and emesis and more unplanned admissions have been observed when compared with a propofol, alfentanil, and an air/oxygen mixture.[59]

Novel analgesic measures have been investigated during oocyte retrieval. Electro-acupuncture has been suggested as alternative to intravenous alfentanil, although both groups also received a paracervical block and the acupuncture group experienced higher degrees of preoperative stress and longer periods of discomfort during oocyte aspiration.[60]

Embryo Transfer

Described as relatively painless, transcervical ET is most commonly performed without analgesia or anesthesia; on rare occasion, intravenous sedation, regional or general anesthesia may be requested. Transabdominal gamete or ETs (ie, GIFT, ZIFT) are usually performed via laparoscopy under local, regional, or general anesthesia. The associated concerns of the laparoscopic technique and the Trendelenburg position should be reviewed; major intraoperative complications associated with laparoscopy are rare but include gastric or intestinal perforation, hemorrhage, pneumothorax, pneumopericardium, mediastinal emphysema, gas embolism, and cardiac arrest.[61]

Postoperative Management

The incidence of anesthetic or surgical complications requiring hospital admission after ART procedures is low. Oskowitz et al[52] reported admission rates after oocyte retrieval and GIFT of 0.16% and 0.18%, respectively. The most common indications for hospitalization included hemoperitoneum and syncope after oocyte retrieval, and nausea, vomiting, and bowel injury after laparoscopic GIFT. Incisional pain, diffuse abdominal pain, uterine cramping, and referred shoulder pain from diaphragmatic irritation occur frequently after laparoscopy, in part from retained intraperitoneal carbon dioxide. Although pain accompanied by nausea is usually a reasonable indication for the use of nonsteroidal anti-inflammatory drugs, these agents are avoided due to changes in the prostaglandin milieu that can affect embryo implantation.[62] Small doses of intravenous fentanyl (25 to 50 μg) or oral acetaminophen with codeine can be used to provide analgesia.

Table 2. *Discharge Criteria for ART Procedures*

1. Alert and oriented to time and place
2. Stable vital signs
3. Pain controlled by oral analgesics
4. Nausea or emesis mild if present
5. Able to walk without dizziness
6. Regional anesthesia
a. Block appropriately resolved
b. Able to urinate (if spinal or epidural)
7. No unexpected bleeding from operative site
8. Given discharge instructions from surgeon, anesthesiologist, reproductive endocrinologist, and nursing and prescriptions
9. Patient accepts readiness for discharge
10. Responsible adult present to accompany patient

Nausea and emesis can also occur; however, exposure to droperidol and metoclopramide should be limited (see above); treatment with nondopaminergic agents can be considered. Before discharge, patients should be able to drink and retain oral liquids, ambulate, and void (Table 2). Patients undergoing anesthesia for ART should receive a follow-up call at 24 hours postprocedure to respond to any questions or complications.

■ Future Considerations

ART procedures are increasingly being used in patients with a broader range of ages and comorbidities. Improvements in ultrasonography and fiberoptic methods for oocyte retrieval and fallopian tube cannulation could potentially make current methods, including laparoscopic interventions, unnecessary, and allow for changes in anesthetic options. The identification of agents and techniques that provide optimal analgesia or anesthesia with negligible impact on ART success is an important process to which anesthesiologists can and should contribute.

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