Purpose

The use of laparoscopic surgical techniques is becoming increasingly prevalent for reproductive manipulations in female nonhuman primates (NHP) in biomedical research. Replacement of laparotomy with laparoscopy fulfills a component of the 3Rs as laparoscopic surgery is a refinement over open techniques. Laparoscopic approaches are also often considered minor procedures thus reducing the number of major surgical procedures an animal will undergo on a protocol and in its lifetime. The Association of Primate Veterinarians (APV) supports the replacement of open surgical techniques with minimally invasive, laparoscopic approaches when possible to minimize pain and distress while reducing post-operative recovery times. The decision to approve and utilize laparoscopic techniques lies with the institutional animal care and use committee (IACUC), the surgeon’s skill with laparoscopy, equipment and establishment of a close working relationship between the veterinary and investigative staff. This document aims to provide NHP researchers, IACUC members, and veterinarians with guidelines for considering and conducting research involving laparoscopic reproductive manipulations in NHPs.

Background

Laparoscopy is a surgical procedure performed in the abdominal cavity through small incisions (usually 0.5–1.5 cm) with the aid of a camera, or laparoscope. Laparoscopy has been used in both human and NHP medicine for a variety of reproductive procedures. Common reproductive manipulations performed via laparoscopy in NHPs include ovarian follicle aspiration with oocyte collection, ovariectomy, diagnostic laparoscopy, and embryo transfer. Laparoscopy is also utilized for more specialized reproductive manipulations, induction of disease models, and therapeutic interventions in the NHP.

Given the smaller incisions when compared to an open laparotomy, there is generally less inflammation and decreased post-operative incision pain. Likewise, there is generally decreased hemorrhage and reduced post-operative infection risk when compared to the same surgical procedures approached by laparotomy. Additionally, the risk of post-operative adhesion formation is decreased. These combine to decrease the overall hospital stay in human patients and, in nonhuman primates, decrease the time to return to social housing.

Training opportunities for laparoscopic interventions are available through veterinary colleges and wet labs at the Academy of Surgical Research’s Annual Meeting. Primate veterinarians experienced in NHP laparoscopic techniques, board certified veterinary surgeons with experience in laparoscopy and collaboration with human surgeons can also be useful sources for training when learning or developing laparoscopic techniques. Additional information about laparoscopic training opportunities is provided in the References section of this document.
IACUC Considerations

The 8th edition of the Guide states, “…major survival surgery … penetrates and exposes a body cavity, produces substantial impairment of physical or physiologic functions, or involves extensive tissue dissection or transection (Brown et al. 1993). Minor survival surgery does not expose a body cavity and causes little or no physical impairment… Laparoscopic surgeries…may be classified as major or minor surgery depending on their impact on the animal (Devitt et al. 2005; Hancock et al. 2005; NRC 2003; Perret-Gentil et al. 1999, 2000). For example, laparoscopic techniques with minimal associated trauma and sequelae…could be considered minor, whereas others…should be considered major. Although minor laparoscopic procedures are often performed on an “outpatient” basis, appropriate aseptic technique, instruments, anesthesia, and analgesia are necessary. Whether a laparoscopic procedure is deemed major or minor should be evaluated on a case-by-case basis by the veterinarian and IACUC.”

The IACUC committee with input from the veterinary staff is tasked with determining whether specific laparoscopic manipulations qualify as major or minor procedures at their institution and at what frequency, within a protocol and within a lifetime, a NHP may undergo such procedures. Depending on the complexity and consequences of the laparoscopic manipulation, a single or multiple laparoscopic procedures may be approved within a protocol and within the lifetime of a research subject. These determinations should be made after careful consideration of the degree of manipulation associated with the procedure and whether major physiologic impairment and/or perioperative and long-term consequences, such as pain and distress, are expected. As a general rule, the APV would suggest that ovarian follicle aspiration with oocyte collection, diagnostic laparoscopy, and embryo transfer would in most cases be considered minor surgery. Ovariectomy, on the other hand, and any other procedures causing physiologic impairment, would be considered major surgery.

Animal Selection

Females NHPs selected for protocols involving laparoscopy are generally sexually mature with or without a history of active reproduction or reproductive manipulation. Routine screening of candidates for protocols involving laparoscopy should include a complete medical history review as well as a physical exam with a complete blood count and chemistry panel, if recent blood work has not been performed. History review should include an evaluation of previous births and reproductive manipulations with special attention paid to any complications or sequelae associated with these events. Abnormalities noted during previous reproductive procedures including aberrant anatomy, adhesions or cysts may preclude assignment of an animal to a study with laparoscopy. A history of a normal menstrual cycle may also be important depending on study aims. Physical examination may include a reproductive evaluation with bimanual (rectal and abdominal) palpation of uterine structures, which normally move freely in the caudal abdomen without restriction. When selecting animals for studies involving laparoscopic manipulations, consideration of the animal’s future use in research and breeding may be warranted.
Procedure considerations

Laparoscopic technique, equipment, and pre-operative care will vary depending on the research goals and procedures being performed. The procedure may be modified for certain species or for animals with previous manipulations. For species that classically develop abdominal adhesions, pre-operative ultrasound may be warranted to determine if a para-midline approach is preferable to avoid existing tissue attachments. Animals that have undergone previous reproductive manipulations or laparotomy may have midline adhesions that necessitate use of a para-midline scope port to allow appropriate visualization (see references).

A variety of intra-operative complications have been linked to laparoscopic manipulation in humans and animals. Complications may be associated with entry of the abdomen, creation of the pneumoperitoneum, positioning, and visualization/manipulation. Port incisions that are too large may result in loss of insufflation and difficulty maintaining appropriate visualization of the reproductive tract. Incisions should be as small as possible to allow placement of the port without damage to the surrounding tissue to minimize CO₂ leakage. Placement of ports with the aid of trocars may result in mechanical trauma including injury to major vessels or the gastrointestinal tract, abdominal wall hematoma, perforated bladder and ureteral injury. The structures listed above may also be damaged during manipulation of the abdominal contents by laparoscopic instruments if care is not taken with tissue manipulation or visualization is poor making identification of abdominal structures difficult. Pneumoperitoneum, created by insufflation with CO₂ gas to improve visualization and manipulation of abdominal contents, has also been associated with intraoperative complications such as respiratory acidosis, deep vein thrombosis, subcutaneous emphysema, gas embolism, reduced dynamic lung compliance, and increases peak inspiratory and plateau pressures (mechanical ventilation is recommended when abdomen is insufflated). In humans, shoulder pain due to irritation of the diaphragm or stretching of the phrenic nerve has also been noted following laparoscopic procedures. Animals in a Trendelenburg position paired with CO₂ insufflation of the abdomen may experience an increase in mechanical impedance to lung inflation, therefore mechanical ventilation is recommended.

Post-surgical procedures

Post-operative monitoring should be provided immediately post-procedure until the patient is returned to its home cage and able to maintain itself consistently in an upright position. Comprehensive post-operative monitoring may be conducted daily for 3-7 days post-procedure with specific evaluation of basic NHP physiology and behavioral parameters. Post-operative analgesia should be provided for 48-72 hours following the surgical procedure.

Short-term complications associated with laparoscopy are generally associated with the surgical incisions; however, post-operative abdominal discomfort or hemorrhage may occur. Incisions should be monitored closely in the post-operative period for erythema, inflammation, and discharge, which may be indicative of an incision site infection. Fascial dehiscence and herniation of abdominal contents through the incision sites are also possible; however due to the small size of the incisions, omentum is generally the only abdominal tissue present in laparoscopic incisional hernias.
Long-term complications associated with laparoscopic procedures center on impaired fertility, endometriosis and adhesion formation. Fertility may be compromised by trauma or damage to the ovaries, oviducts, uterus or associated vasculature during the laparoscopic procedures. For any protocols known to compromise normal female reproductive anatomy, future reproductive use of the animal should be considered prior to assignment to the protocol and before returning the animal to a breeding situation. Adhesion formation is a common sequela to laparoscopic reproductive manipulation in NHPs. Adhesions are generally minor involving small omental attachments to the ovaries, uterus or abdominal port sites. More extensive adhesions are possible and may distort normal reproductive anatomy; this should be evaluated during follow-up physical examinations, bimanual palpations and reproductive ultrasounds. Thorough flushing of the abdomen following laparoscopic manipulation to remove blood and extraneous fluid may reduce the risk of adhesion formation; this may also reduce the risk of endometriosis development in the case of transuterine laparoscopically-guided manipulations (e.g. uterine biopsy).

References