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Original Article

The Impact of Carbon Dioxide Pneumoperitoneum on Ovarian Ischemia-Reperfusion Injury during Laparoscopic Surgery: A Preliminary Study

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ABSTRACT **Study Objective:** To investigate whether carbon dioxide pneumoperitoneum causes ischemia-reperfusion injury to the ovaries during laparoscopic surgery.

Design: A prospective controlled clinical study (Canadian Task Force classification II-1).

Setting: A tertiary academic center.

Patients: Premenopausal women who underwent hysterectomy with bilateral salpingo-oophorectomy (HSO) via open abdominal and laparoscopic approaches between 2014 and 2015.

Interventions: In both surgical approaches, unilateral oophorectomy was performed immediately after abdominal entry, and the remaining contralateral ovary was excised at the end of the hysterectomy in order to compare the effect of these surgical procedures on ovarian tissue. Additionally, plasma samples were collected at the following time points: (1) before abdominal entry, (2) at the end of hysterectomy, and (3) before contralateral oophorectomy. Plasma samples were assessed for biochemical oxidative stress markers malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG). Ovarian tissue samples were assessed for MDA and further evaluated for ischemia-reperfusion injury using a histologic scoring method.

Measurements and Main Results: Twenty premenopausal women undergoing HSO via open abdominal surgery (n = 10) and laparoscopy (n = 10) were included. Baseline characteristics (age, body mass index, parity, and gravida) and operative data (operative time, estimated blood loss, and intraoperative complication) were similar between groups. Perioperative plasma MDA levels, histologic scores, and tissue oxidative stress markers did not show a significant difference in either group or between groups. However, plasma 8-OHdG levels were significantly different when the second sample in the abdominal HSO group was compared with the first sample in the abdominal HSO group and the third sample in the laparoscopic HSO group (p = .012 and .001, respectively).

Conclusion: Carbon dioxide pneumoperitoneum does not cause ischemia-reperfusion injury in the human ovaries at clinically safe levels of intra-abdominal pressure. Journal of Minimally Invasive Gynecology (2017) ■■, ■■–■■

Keywords: Pneumoperitoneum; Intra-abdominal pressure; Ovarian injury; Ischemia-reperfusion; Oxidative stress

In the last 3 decades, laparoscopy has become an essential tool in the diagnosis and treatment of several gynecologic pathologies. Its well-established advantages over laparotomy ignited worldwide application of laparoscopy as the primary choice of surgical approach in both benign and malignant conditions [1]. Laparoscopy is currently the preferred surgical route for the diagnosis and treatment of infertility-related issues such as endometriosis, uterine myomas, and ovarian and tubal pathologies [2,3]. However, it has been

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questioned whether carbon dioxide (CO_2) pneumoperitoneum itself during laparoscopy can cause ovarian damage because of ischemia-reperfusion injury and jeopardize reproductive potential.

In previous studies, increased intra-abdominal pressure (IAP) after CO_2 insufflation has been reported to reduce the blood flow to solid organs by 10% to 80% during laparoscopy and normalizes with desufflation of the abdominal cavity [4]. These hemodynamic changes, in terms of hypoperfusion followed by reperfusion, represent a typical model of the ischemia-reperfusion phenomenon, which leads to the production of reactive oxygen species (ROS). Excessive production of ROS is widely recognized as the central cause of several pathologies because of its impact on cellular injury and death [5]. Although in some experimental animal studies CO_2 pneumoperitoneum has been shown to be associated with a significant level of ovarian injury caused by oxidative stress even at safe levels of IAP [6–8], there has been no clinical investigation showing its effects in human ovaries.

As a result of these emerging concerns related with pneumoperitoneum-induced ovarian injury, in this study we aimed to investigate whether CO_2 pneumoperitoneum has a detrimental impact on human ovaries during laparoscopic surgery by assessing biomarkers of oxidative stress in human plasma and tissue samples.

Materials and Methods

Ethical Approval

Institutional review board approval was obtained from the Ege University Ethical Committee (institutional review board number 12-6/13).

Patients

Premenopausal patients undergoing hysterectomy with bilateral salpingo-oophorectomy (HSO) via laparoscopy or open abdominal surgery for benign indications were invited to participate. The exclusion criteria for the study were smoking; cardiovascular disease; pulmonary disease; hepatic or renal dysfunctions; a previously known ovarian pathology or ovarian surgery; gynecologic malignancy; and factors that could complicate the surgical procedures and timely removal of the ovaries such as morbid obesity, previous abdominal surgery, and intra-abdominal adhesions.

Surgical Methods and Plasma and Tissue Sample Collections

All operations were performed under endotracheal general anesthesia in the dorsal lithotomy position. Patients were administered a single dose of 1 g cefazolin sodium for prophylaxis within 1 hour before surgical incision. Hemodynamic (arterial blood pressure and cardiac rhythm) and respiratory (arterial blood gas values, airway pressures, dynamic pulmonary compliance, peripheral pulse oximetry, and end-tidal CO_2 level set at 35–45 mm/Hg) parameters were continuously monitored throughout the surgeries. The surgical steps and sample collection time points for both groups are shown in Figure.

In the laparoscopic HSO group, after the induction of anesthesia, the first plasma sample (Lp_1) was obtained for baseline, and an umbilical skin incision was performed. Pneumoperitoneum was established using dry, nonheated CO_2 insufflation through a Veress needle. A 10-mm trocar was inserted into the abdominal cavity through the umbilical incision for the laparoscope. Subsequently, three 5-mm ancillary trocars, 2 on the lower abdominal quadrants and 1 on the left upper quadrant, were introduced to the abdominal space under direct optic visualization. IAP was set at 14 mm Hg and maintained with a gas insufflator (Endoflator; Karl Storz Endoscopy, Tuttlingen, Germany). Immediately after the port placement, unilateral oophorectomy was performed, and ovarian biopsies were obtained. The operation continued with ligation and transection of the contralateral utero-ovarian ligament and the bilateral round ligaments. The contralateral infundibulopelvic ligament, which contains the main vascular supply for the contralateral ovary, remained intact. Subsequently, anterior and posterior leaflets of the broad ligament were identified and dissected, and the bladder was placed away from the lower uterine segment. At this point, a second plasma sample (Lp_2) was obtained to reflect the ischemic status caused by the increased IAP, and, subsequently, pneumoperitoneum was released. After desufflation, the hysterectomy procedure was completed vaginally. At the end of vaginal cuff closure, a third plasma sample (Lp_3) was collected to represent the reperfusion period. At the final step, pneumoperitoneum was reestablished, the remaining contralateral ovary was removed immediately, and biopsies were obtained for histologic and biochemical analyses.

Likewise, in the abdominal HSO group, after the induction of anesthesia, a baseline plasma sample (Ap_1) was obtained, and a Pfannenstiel incision was performed. Immediately after abdominal entry, unilateral oophorectomy was performed, and tissue samples were sent for biochemical and histopathological evaluations. Subsequently, the contralateral utero-ovarian ligament and the bilateral round ligaments were ligated and transected. Anterior and posterior leaflets of the broad ligament were identified and dissected, and the bladder was positioned away from the lower uterine segment. The bilateral uterine vascular pedicles and the sacrouterine ligaments were ligated and transected. After circumferential colpotomy, the uterus was removed, and the vaginal cuff was closed with separated sutures. Before the removal of the remaining contralateral ovary, a second plasma sample (Ap_2) was obtained. At the final step, oophorectomy was performed, and the abdominal incision was closed appropriately.