Original Article

Low-pressure pneumoperitoneum reduces influence on ovarian hormones in infertile women: a randomised trial

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Background: Pneumoperitoneum is commonly used in laparoscopic gynecological surgery. This study investigated the effect of carbon dioxide (CO_2) pneumoperitoneum pressure on ovarian function following laparoscopic surgery in infertile women.

Methods: A total of 424 infertile patients were allocated to 4 groups according to different CO_2 pneumoperitoneum pressures undergo laparoscopic surgery. Complications and the levels of serum estradiol (E_2), progesterone (P), luteinizing hormone (LH), testosterone (T), and follicle-stimulating hormone (FSH) were observed and measured. Ovarian function was also evaluated by using mean ovarian volume, maximal ovarian volume, mean follicle number, and maximal follicle diameter.

Results: A total of 118 cases were included and their data were retrospectively analyzed. Complications were observed in all groups with the highest incidence in participants receiving 15–16 mmHg CO_2. Pneumoperitoneum increased the levels of E_2, FSH, and LH ($P<0.05$) with increasing pressure, especially in the first menstrual period after surgery, and these levels had returned to normal by the third menstruation; the levels of P and T were not affected.The MOV, MFD and MFN remained unchanged after surgery in four groups, and the menstrual cycle after surgery at 1 month in group D delayed ($P<0.05$).

Conclusions: The use of CO_2 for pneumoperitoneum affects the levels of E_2, LH, and FSH during the first menstruation after laparoscopic surgery in a pressure-dependent manner and the impact vanishes by the third menstruation.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100046221.

Keywords: Carbon dioxide (CO_2); pneumoperitoneum; laparoscopic surgery; ovarian hormones

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Introduction

In recent years, laparoscopic surgery has become one of the most important diagnostic and therapeutic approaches in gynecological surgery. The surgery can improve the efficiency and maintain hemodynamic stability in laparoscopy for gynecological diseases (1). This minimally invasive therapy requires pneumoperitoneum for adequate visualization and operative manipulation. Carbon dioxide (CO_2) is the most commonly used gas to inflate the peritoneum, because of its high diffusibility and rapid absorption and excretion. Compared with open surgical procedures, this technique potentially offers shorter operative time and hospital stay, earlier recovery, and less pain and pelvic adhesions (2,3).

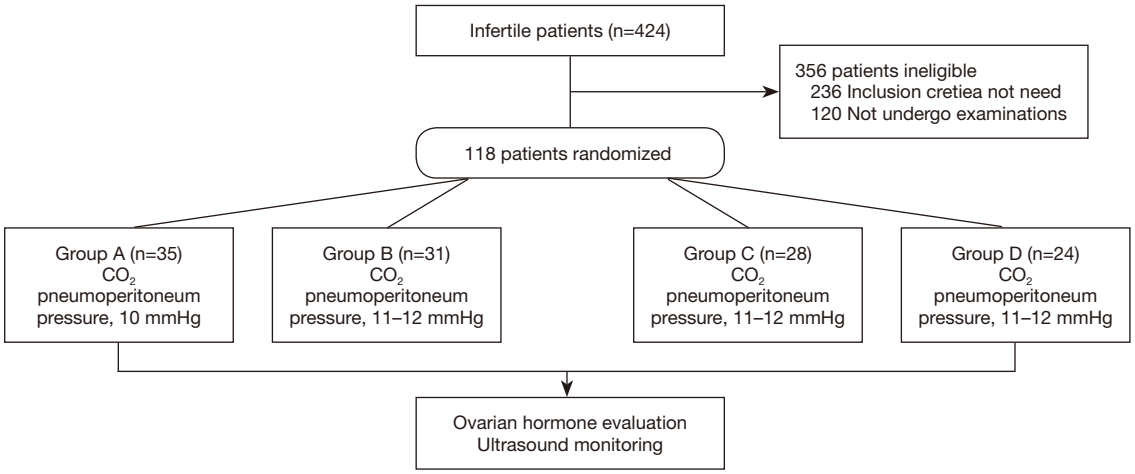

Figure 1 Study profile.

However, insufflation of CO_2 into the peritoneum may lead to alterations in the acid-base balance, and cardiovascular and pulmonary physiology. Mastroyannis *et al.* reported the effects of CO_2 pneumoperitoneum pressure on rabbit follicular oocytes and early embryonic development using the animal model of pneumoperitoneum. They found that the duration of pneumoperitoneum, irrespective of type of gas used, was negatively correlated with success of embryonic development (4).

There are many reports on the safety of low CO_2 pneumoperitoneum pressure (5,6). The benefits of laparoscopic surgery include reduced blood loss, fewer transfusions, and shorter hospital stay. Peng *et al.* found that CO_2 pneumoperitoneum did not raise the incidence rate of bacterial translocation under laparoscopy surgery (7). Chen *et al.* showed that CO_2 pneumoperitoneum did not affect expression of the cellular proliferation marker Ki67 in an orthotropic xenograft nude mouse model of human renal cell carcinoma (8). Contrastingly, high pressure CO_2 pneumoperitoneum was found to induce oxidative damage and apoptosis in rabbit kidneys with severe hydronephrosis (9). However, there has been little exploration of the clinical effects of low CO_2 pneumoperitoneum pressure in post obstetric surgery patients. Akdemir *et al.* demonstrated that CO_2 pneumoperitoneum does not cause ischemia-reperfusion injury in premenopausal human ovaries at clinically safe levels of intra-abdominal pressure (14 mmHg) (10). However, the effect of different CO_2 pneumoperitoneum pressure on ovarian function in laparoscopy has not been reported. Therefore, it is very important for gynecologists to fathom the effect of pneumoperitoneum pressure on reproductive-age patients.

The purpose of our study was to evaluate the effect of CO_2 pneumoperitoneum pressure on ovarian hormones in infertile women. The findings were intended to contribute to the development of a standard of CO_2 pneumoperitoneum pressure for infertile women undergoing laparoscopic surgery and reduce the adverse effects of the surgery.

We present the following article in accordance with the CONSORT reporting checklist (available at http://dx.doi.org/10.21037/apm-21-476).

Methods

Participants

From April 2009 to May 2013, a total of 424 women diagnosed infertile at the Institute of Obstetrics and Gynecology were screened for this study (*Figure 1*). Patients were included if their infertility was caused by pelvic adhesions, tubal factors, or unexplained, and were followed up for 3 menstrual cycles following surgery.

Patients with endocrine-related diseases, such as endometriosis and polycystic ovary syndrome (PCOS), were excluded. Participants who dropped out during the course of study were also excluded. The excluded cases were as follows: 106 were diagnosed with endometriosis upon surgery; 80 were diagnosed with PCOS, 50 had ovarian cysts detected during surgery (ovarian endometrial cyst, 26 cases; teratoma, 18 cases; corpus luteum cyst, 6 cases). A total of 120 cases were excluded who did not undergo blood

Table1 Baseline characteristics of the study sample

Characteristic	Group A (n=35)	Group B (n=31)	Group C (n=28)	Group D (n=24)
Age (years)	26.25±4.7	25.93±4.68	26.53±5	29.13±2.75
Body mass index (kg/m^2)	21.27±2.36	21.89±2.45	22.36±2.09	A 21.85±2.05
Surgical time (minutes)	60.34±15.33	62.1±16.71	62.69±18	94.55±11.7[a]
Hospital days (days)	4.17±0.77	4.37±0.81	4.19±0.76	4.95±0.58
Number of prior abdominal surgeries (range)	0–1	0–2	1–2	1–3
Inoperative adhesion (%)	11.4	19.3	17.9	37.5[a]

[a], P<0.05 *vs.* group A, B, and C.

draw or ultrasound examination.

A total of 118 patients (aged 18–39 years) met the inclusion criteria and were retrospectively analyzed. Among them, 70 participants underwent laparoscopic surgery for pelvic adhesions, 20 underwent tubal colostomy, 6 underwent tubal fimbria angioplasty, and 22 underwent laparoscopic surgery for detection. According to the CO_2 pressure applied in laparoscopic surgery, and the volume of insufflation of CO_2 was determined by pneumoperitoneum pressure indicator (Olympus UHI-4; Japan), participants were divided into 4 groups [A, 10 mmHg (n=35), B, 11–12 mmHg (n=31), C, 13–14 mmHg (n=28), and D, 15–16 mmHg (n=24), respectively] (*Figure 1*). All surgical procedures were performed by the same surgeons. Written informed consent was provided by every participant and the study protocols were approved by the Ethics Committee and Institutional Review Board of the Maternal and Child Hospital (No. 81), Guiyang. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Ovarian hormone evaluation

The ovarian hormones estradiol (E_2), progesterone (P), luteinizing hormone (LH), testosterone (T), and follicle-stimulating hormone (FSH) were detected by radioimmunoassay. These hormones were assessed before and on days 3 and 5 of the first and third menstrual cycles after surgery.

Ultrasound monitoring

Uterus and bilateral annexes were detected via vaginal examination on the first 3–5 days of menstruation before and after surgery. A 6.0 MHz vaginal probe of B-mode ultrasound (Sonolayer SSA-220A, Toshiba, Tokyo, Japan) was used for examination. The number and diameter of follicles and diameter of ovaries were measured at 3 time points (T0, before operation; T1, 1 month after operation; T2, 3 months after operation). Ovarian volume was calculated as previously described (11). Ovarian function was also evaluated using mean ovarian volume (MOV, the average volume of both ovaries), maximal ovarian volume (MaxOV, the volume of the largest ovary), mean follicle number (MFN, the mean number of bilateral ovarian follicles), and maximal follicle diameter (MFD, the dominant follicle diameter).

Statistical methods

Measurements were expressed as means ± SD and/or median and range. Means were compared using the Student's *t*-test or 2-way analysis of variance (ANOVA) with the corresponding post-test. All statistical tests were 2-tailed and P value <0.05 was considered statistically significant. All data were analyzed using the software SPSS 19.0 (SPSS, Inc., IBM, Chicago, IL, USA).

Results

Participants and surgical complications

A total of 118 patients were included in this study. The mean age of the participants was 27.2±4.6 years (18–36 years). The mean surgery time was 89±16 min (35–120 min). The total numbers of participants were 35, 31, 28, and 24 in groups A, B, C, and D, respectively. Length of hospital stay was not different among the 4 groups (P>0.05). Group D had the longest surgical time, and also had the highest frequency of pelvic adhesion (37.5%, *Table 1*).

Table 2 Surgery related complications in four groups

Grade	Description	Group A (n=35)	Group B (n=31)	Group C (n=28)	Group D (n=24)
1	Treatment of complication requires only minor invasive procedures that can be done at the bedside	Pain of shoulder 1	Pain of shoulder 2 Nausea, vomiting 1	Pain of shoulder 1 Pnenmohypoderma 1	Pnenmohypoderma 1
2	Complication requires pharmacologic treatment with drugs	0	Nausea, vomiting 1	Pain of shoulder 2 Nausea, vomiting 1	Pain of shoulder 4 Nausea, vomiting 2 delayed wound heals 1
3	Requires management by an endoscopic, interventional procedure	0	0	Pain of shoulder 1 Nausea, vomiting 2	Nausea, vomiting 3 Delayed wound heals 1
4	General anesthesia is required to treat complication	0	0	0	0
5	General anesthesia is required to treat complication and single organ failure has developed	0	0	0	0
6	Postoperative death occurred	0	0	0	0
Sum		1 (2.86%)	4 (12.9%)	8[a] (28.6%)	12[a] (50%)

[a], P<0.05, *vs*. group A.

Surgical complications were graded according to the Accordion Severity Grading System (12) and the results are summarized in *Table 2*, including pneumohypoderma, shoulder pain, delayed wound healing, and postoperative nausea and vomiting. The incidences of complications in group A, B, C, and D were 2.86%, 12.9%, 28.6%, and 50%, respectively, and were significantly higher in group C and D than in group A (P<0.05). No severe complications were observed in all groups, such as severe infection or damage to adjacent organs and blood vessels.

Ovarian hormones E_2, FSH, LH, P, and T

Preoperative levels of ovarian hormones were within the normal range and were similar among the 4 groups. The E_2 decreased significantly in the first menstrual period following surgery as compared with before surgery (P<0.05) and returned to the preoperative levels in the third menstrual period (*Figure 2A*). It trended to decrease with increasing CO_2 pressure. After surgery, serum E_2 was the lowest in group D, although it was not significantly different among the 4 groups (P>0.05, *Figure 2A*).

Levels of LH and FSH were higher at the first menstrual period after surgery than before surgery (P<0.05). Both had returned to normal range at the third menstrual period (*Figure 2B*,*C*). The concentrations of LH and FSH showed an increasing tendency with increasing CO_2 pressure, especially in group D, where they were statistically higher than in the other 3 groups (P<0.05) (*Figure 2B*,*C*). The levels of P and T did not show significant change after surgery and CO_2 pressure did not affect the levels of these hormones (P>0.05, *Figure 2D*,*E*).

MOV, MFN, and MFD

We then surveyed the change of ovarian structures with B-mode ultrasound at day 5 of the menstrual cycle. The MOV, MFD, and MFN remained unchanged after surgery (*Figure 3A*,*B*,*C*, P>0.05), although MFN in group D showed a statistically insignificant decrease at 1 month (P>0.05, *Figure 3C*).

Length of menstrual cycle

We followed up the menstrual cycle after surgery and found that the menstrual period of participants in group D were delayed at 1 month post operation (P<0.05, *Figure 3D*). However, it had recovered to normal range at the third

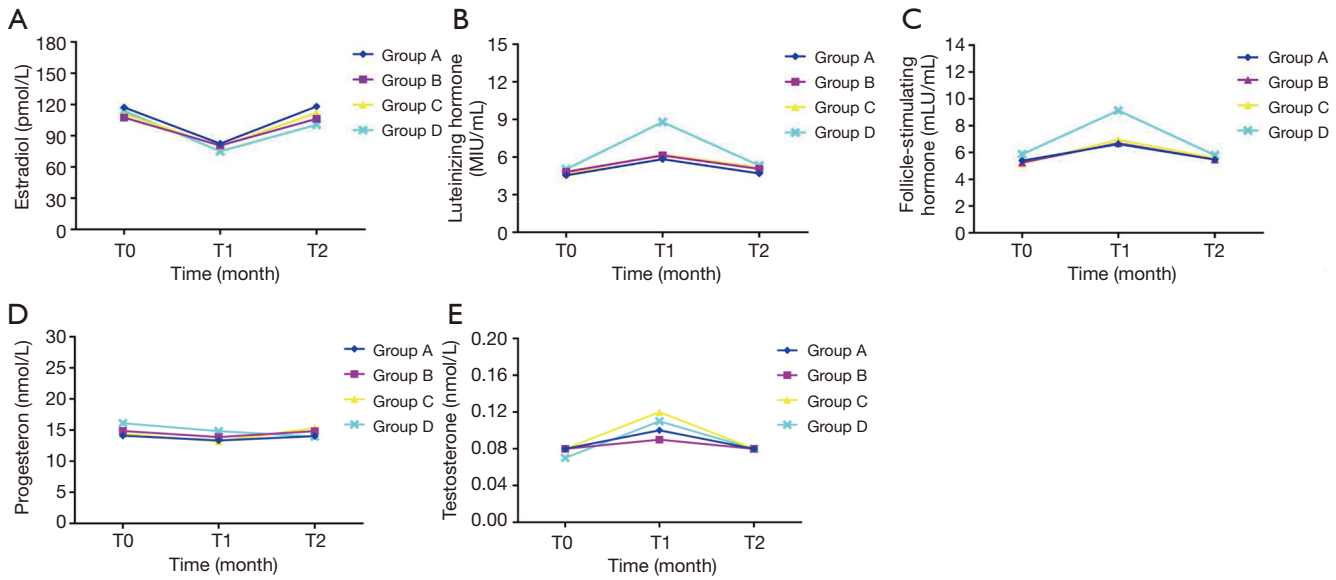

Figure 2 The levels of ovarian hormones before and after surgery under different CO_2 pneumoperitoneum pressures. (A) Estradiol; (B) luteinizing hormone; (C) follicle-stimulating hormone; (D) progesterone; and (E) testosterone. T0, before operation; T1–2, one and three months after operation. CO_2, carbon dioxide.

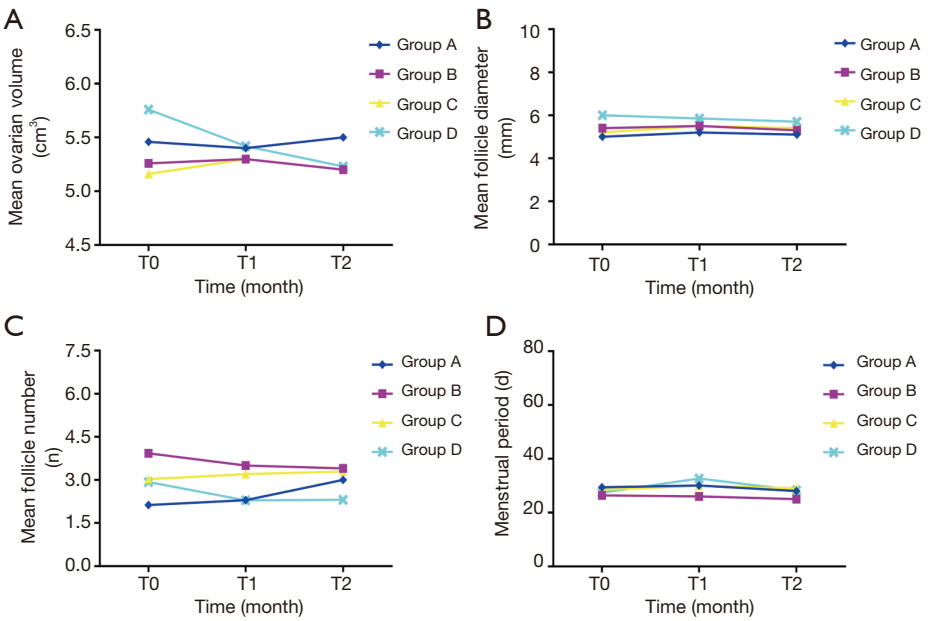

Figure 3 The MOV, MFN, MFD, and menstrual period before and after surgery under different carbon dioxide pneumoperitoneum pressures. (A) Mean ovarian volume; (B) mean follicle diameter; (C) mean follicle number; (D) menstrual period (day). T0, before operation; T1–2, 1 or 3 months after operation. MOV, mean ovarian volume; MFN, mean follicle diameter; MFD, mean follicle diameter.

menstrual period. Within 1 year, 46 participants were successfully pregnant after surgery.

Discussion

Increased intra-abdominal pressure used in laparoscopy resulting from pneumoperitoneum may lead to systemic effects, such as acid-base imbalance, blood gas alterations, and pulmonary disease, cardiovascular disease, pneumothorax, mediastinal emphysema, air embolism, and acute respiratory distress syndrome (ARDS) (13,14). We reviewed the literature for clinical and laboratory studies on the currently used laparoscopic insufflation gases, and CO_2 showed adverse effects on respiration and circulation (15).

Eleftheriadis *et al.* found when pneumoperitoneum pressure was up to 15 mmHg, bacteria could diffuse to other organs in the abdominal cavity (16). Marana *et al.* confirmed that CO_2 pneumoperitoneum pressure affected stress-related neuroendocrine hormones after comparing the level of stress hormones, plasma epinephrine, norepinephrine, and epinephrine after laparoscopy, mini laparotomy, and laparotomy (17). However, the range of pneumoperitoneum pressure that is safe for ovarian function has not been well defined. Bogani *et al.* compared low (LPP 8 mmHg) *vs.* standard pneumoperitoneum pressure (SPP 12 mmHg) during mini-laparoscopic hysterectomy (MLH), and found there was less shoulder-tip pain in LPP (18). In our study, low CO_2 pneumoperitoneum pressure was found to be safer and feasible for surgery. No severe complications, such as infection, adjacent organ damage, abdominal vascular injury, and drain off into the abdominals, occurred at low pressure. Conversely, under high pressure (15–16 mmHg), more complications were observed, which was similar to earlier works (18).

Our analysis showed that CO_2 pressure of CO_2 has some effects on ovarian hormones, especially in the first postoperative menstrual period. When the pressure applied exceeded 15 mmHg, the serum LH and FSH increased significantly in the first menstrual period. At the highest pressure, patients' menstrual cycles were extended. Recently, a prospective study showed that CO_2 pneumoperitoneum caused acute injury to the retained kidney after laparoscopic donor nephrectomy (19). Our data showed that Group D had the longest surgical time, and the highest incidence of pelvic adhesion (37.5%). We speculate that high pressure may reduce ovarian blood supply during operation, and this adverse effect would prolong surgical time and increase surgical difficulty.

Meanwhile, we also found that increased pneumoperitoneum pressure might result in reduced follicle numbers. These clinical observations and laboratory data suggest that high pneumoperitoneum pressure may adversely affect follicular development during the cycle.

Measurement of FSH and LH during the cycle can reflect ovarian reserve (20). Based on the recent result that high CO_2 pneumoperitoneum pressure reduced splanchnic blood (19,21), it is likely that when CO_2 pneumoperitoneum pressure exceeds 16 mmHg, it might affect the ovarian blood supply and cause a transient ischemia-reperfusion, affecting follicular development and leading to temporary follicular dysplasia. However, this impact is likely short-lived and would vanish soon after surgery. As a consequence, we observed that the ovarian hormone levels had returned to previous levels by the third menstrual period.

Previously, ovarian surgery was found to have various impacts on the menstrual cycle and ovarian function. For example, Sayegh *et al.* reported on 87 reproductive-aged women who had undergone pelvic surgery for indications including endometriosis, infertility, and pelvic pain; the result showed conservational ovarian surgery had no significant effects on ovulatory and menstrual function over a prolonged follow-up period (22). Zhang *et al.* found that ovarian biopsy/scratch could promote follicle development *in vivo* (23). In addition, surgical excision of endometriomas acutely impairs ovarian function (24) and hemostatic methods during surgery affect ovarian function (25).

We further analyzed the characteristics of participants in group D. Since frequent intraoperative adhesions occurred in the group, it is likely that the ovarian function affected by high CO_2 pneumoperitoneum pressure resulted from the adhesions as well as from adhesion-induced release of inflammatory factors. Therefore, for patients with severe adhesions, factors other than pneumoperitoneum pressure should be taken into consideration. Based on our data, it is reasonable to interpret that CO_2 pneumoperitoneum pressure below 16 mmHg is safer for preservation of ovarian function. Base on the reported researches (15,26), N_2O (nitrous oxide) has only weak hemodynamic effects. It seems to be the alternative gas for insufflation into the peritoneum. Other gases such as helium, air, nitrogen and argon, which have no significant advantage over CO_2 or N_2O. Menes T reviewed previous studies and concluded the effect of CO_2 insufflation on acid-base changes usually are mild (15).

However, further exploration is required on the impact of CO_2 pneumoperitoneum pressure on acid-base changes and blood supplying the ovaries, oocyte quality, subsequent pregnancy in multi-center, large-cohort studies.

Conclusions

Our work demonstrated that low-pressure pneumoperitoneum in laparoscopic operation has less adverse impacts on ovarian function and a lower complication rate, suggesting that CO_2 pressure below 16 mmHg during laparoscopy for infertility patients is worthy of recommendation. However, this was a single center-, small-scale retrospective study, and the conclusions need to be validated in multi-center, large scale, and prospectively designed studies.

Acknowledgments

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Footnote

Trial Protocol: Available at http://dx.doi.org/10.21037/apm-21-476

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at http://dx.doi.org/10.21037/apm-21-476

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-21-476

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-476). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee and Institutional Review Board of Maternal and Child Hospital (No. 81), Guiyang and written consent was provided by every participant. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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