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GENERAL GYNECOLOGY

Compartment syndrome after gynecologic laparoscopy: systematic review of the literature and establishment of normal values for postoperative serum creatine kinase and myoglobin levels

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Abstract
Purpose To evaluate published evidence in the literature on compartment syndrome (CS) in association with gynecologic surgery and to establish postoperative normal values for serum creatine kinase (CK) and myoglobin.
Methods The present study consists of a case report of a patient with CS, a systematic review including 37 studies and 86 patients with CS, and a retrospective cohort study of 300 patients undergoing various types of laparoscopy for benign or malignant diseases in order to establish postoperative normal values.
Results We report on a patient with early-stage ovarian cancer, who developed CS after laparoscopic surgery with massively elevated serum CK and myoglobin levels, i.e., 1109 U/L and 18151 µg/L, respectively. In our systematic review, median serum CK and myoglobin levels among women with CS were 19,223 (177–27,412) U/L and 1248 (285–1360) µg/L, respectively. In our cohort study, the median postoperative serum CK and myoglobin levels were 68 (14–1576) U/L and 45 (14–1040) µg/L, respectively. The 95th and 99th percentile of serum CK and myoglobin levels were 158 and 391.5 U/L, and 152.3 and 298.9 µg/L, respectively.
Conclusion Markedly elevated postoperative serum levels of CK and myoglobin levels might raise the suspicion for CS and could therefore aid in the rapid diagnosis of CS.

Keywords Compartment syndrome · Case report · Systematic review · Creatine kinase · Myoglobin

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Introduction

The term compartment syndrome (CS) describes a state of substantial tissue damage to muscles and nerves in response to a pathologic pressure increase within a confined inelastic space [1]. CS may develop in various anatomical locations and is mostly an acute event, progressing rapidly in response to an injury or a prolonged state of constant pressure [2]. Events typically associated with CS are skeletal trauma, muscular trauma, and fluid accumulation within a confined space such as hemoperitoneum [1, 2]. However, CS can also occur after prolonged surgical procedures mostly in patients aligned in a lithotomy position. While some cases of abdominal CS in the field of obstetrics and gynecology have been reported [3], most cases after gynecologic surgeries occur in otherwise healthy legs, also termed, well leg CS [4–21]. CS can lead to a loss of function of the affected leg, amputation, or even death by subsequent multi-organ failure [1, 2].

CS is a rare but devastating event in gynecologic surgery. Due to its rarity, the incidence of CS can only be estimated on the base of case reports, reviews, and questionnaires. It has been reported to vary between 0.028% for gynecologic surgeries in general and 0.067–0.38% for surgeries lasting more than 180 min, in particular [2]. Surgeons have to be aware of CS as a potentially lethal complication of gynecologic surgery, especially after complex and long procedures. Prior to such surgery, patients therefore need to be counseled accordingly. In addition, prevention strategies such as compression stockings and time limits of surgical procedures may be applied, although robust scientific evidence for their effectiveness is lacking [1, 2].

A number of risk factors for the development of CS have been identified including lithotomy position, prolonged duration of surgery, intraoperative hypotension and hypovolemia, cardiovascular disease, and diabetes mellitus [1, 2, 4–8]. Regarding the duration of surgery, it has been shown that while some cases of CS might occur after short-lasting surgical procedures, most cases of CS have been observed in surgical procedures >180 min, suggesting that this is a reasonable threshold for defining an elevated risk of CS [1, 2].

Intraoperative and postoperative monitoring for early signs of CS including measurement of intracompartmental pressure (ICP) has been suggested, although based on the invasiveness of the intervention and the rarity of CS, the number needed to treat is enormously high. Thus, measurement of ICP has not been adopted into clinical practice. Suspicion for CS is mostly raised clinically, i.e., when typical signs and symptoms occur such as severe and otherwise unexplainable leg pain. Other symptoms are pain on passive stretch in the involved compartment, paresthesia and, in rare cases and at late stages of CS, pallor and paresis of extremities [22].

Measurement of serum parameters would be an ideal tool for both the risk evaluation and the early diagnosis of CS, especially in sedated patients. Creatine kinase (CK) is a marker of damage of CK-rich muscle tissues such as in myocardial infarction, rhabdomyolysis, muscular dystrophy, or autoimmune myositis [23]. Myoglobin is an iron- and oxygen-binding protein found in the muscle tissue and is the primary oxygen-carrying pigment. Elevated serum levels of myoglobin are exclusively found in the bloodstream after muscle injury [24]. Preliminary data in the literature suggest that both CK and myoglobin are elevated in patients with CS [5, 10, 20].

In our department, we observed a case of CS in September 2015 in a patient with early-stage ovarian cancer. After laparoscopic staging with omentectomy, appendectomy, peritoneal biopsies, pelvic and paraaortic lymphadenectomy, CS was suspected based on severe pain in the lower extremities. ICP, serum CK, and myoglobin were elevated, and prompt fasciotomy was initiated. Based on this index event, we discussed the measurement of serum CK and myoglobin as potential early detection markers of CS and included the measurement of both serum parameters after laparoscopy into our daily clinical practice.

We became aware of the fact that there are no established postoperative CK and myoglobin normal values in order to reliably discriminate between normal and elevated levels indicating an increased risk of CS. Therefore, we performed a systematic review of the literature on CS after gynecologic surgeries focusing on serum CK and myoglobin levels and analyzed CK and myoglobin serum levels in our series of patients undergoing gynecologic laparoscopy.

Materials and methods

We performed a systematic literature search of the databases PubMed and Cochrane Central Register of Controlled Trials (search date 19-01-2017) using search terms related to CS and gynecologic surgery. All abstracts of the studies identified by this search strategy were screened for the inclusion criteria of this literature review, i.e., quantitative reports of women undergoing gynecologic surgery and occurrence of CS in the described patients or in a population of described patients. Studies not reporting on CS or studies reporting on CS after non-gynecologic surgeries were excluded. Subsequently, we retrieved the full-text versions of all studies fulfilling the inclusion criteria. These studies were then analyzed in full. Studies were categorized into case reports, retrospective cases series, retrospective cohort studies, and prospective cohort studies. Authors were not contacted to acquire further information. We included a case report of a patient diagnosed with CS in our department.

In a monocentric cohort study, we included a series of 300 consecutive patients undergoing gynecologic laparoscopy. There were no inclusion or exclusion criteria other than undergoing a gynecologic laparoscopy. The institutional review of the Ordensklinikum Linz approved the present study [Institutional review board (IRB) number 3/2017]. All 300 patients were treated at the Ordensklinikum Linz, Linz, Austria, between November 2015 and January 2017. Patients undergoing laparoscopy were operated upon in general anesthesia in dorsal lithotomy position. The time of the beginning of surgery and the time of the end of surgery were documented according to our department's standard operating procedures.

Serum CK and myoglobin levels were measured after surgery using commercially available test kits (G65502, Abbott Laboratories Diagnostics Division, Abbott Park, IL, and G59014, Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA). Assays were run on the ARCHITECT c System^{TM}. The manufacturer claims normal values of 1–145 U/L and 20–106 µg/L for serum CK and myoglobin levels, respectively.

Statistics

After testing for normality using the Kolmogorov–Smirnov test, values are given as medians (range). The 95th and 99th percentile with the respective 95% confidence intervals are provided. Parameters between two groups were compared using Mann–Whitney *U* tests. Parameters between more than two groups were compared using one-way ANOVA on ranks. In a univariate analysis, continuous parameters were compared using Pearson's correlation coefficient. In a multivariate analysis, continuous parameters were compared using Cox regression analysis. *p* values of <0.05 were considered statistically significant. For statistical analysis, we used SPSS statistical software system (SPSS 23.0; SPSS Inc., Chicago, IL, USA).

Results

Case report

A 45-year-old patient with a unilateral adnexal tumor underwent unilateral adnexectomy demonstrating serous ovarian cancer FIGO stage I, G1. Subsequently, 7 days later, a laparoscopic staging with omentectomy, appendectomy, peritoneal biopsies, pelvic and paraaortic lymphadenectomy was performed in September 2015. The duration of surgery was 5 h and 16 min. Postoperatively, the patient developed severe pain in both lower legs. Serum CK and myoglobin levels were massively elevated, i.e., 1109 U/L and 18151 µg/L, respectively. Measurement of intracompartment pressure showed a value of 70 mmHg. The diagnosis of an acute compartment syndrome was established, and immediate fasciotomy in both lower legs was performed (Fig. 1). Based on this index event, we performed serum CK and myoglobin measurements routinely after all laparoscopies starting in November 2015.

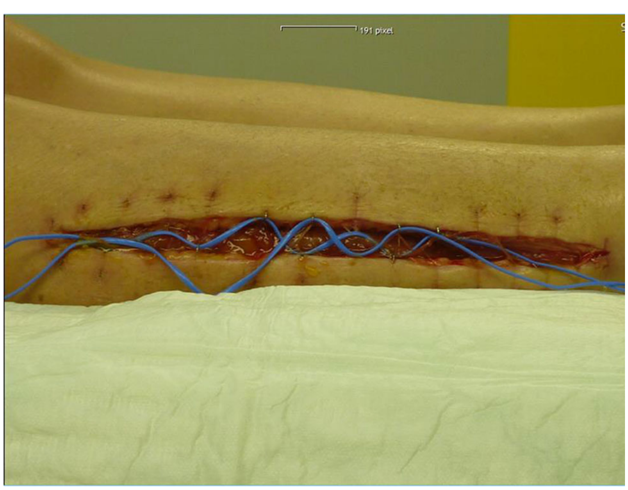

Fig. 1 A colored photograph of the patient with compartment syndrome after undergoing fasciotomy

Systematic review of the literature

In a systematic literature search of the databases PubMed and Cochrane Central Register of Controlled Trials (search date 19-01-2017) using the search terms "gynecologic surgical procedures" (MeSH Terms) OR ["gynecologic" (All Fields) AND "surgical" (All Fields) AND "procedures" (All Fields)] OR "gynecologic surgical procedures" (All Fields) OR ["gynecologic" (All Fields) AND "surgery" (All Fields)] OR "gynecologic surgery" (All Fields)] AND ["compartment syndromes" (MeSH Terms) OR ["compartment" (All Fields) AND "syndromes" (All Fields)] OR "compartment syndromes" (All Fields) OR ["compartment" (All Fields) AND "syndrome" (All Fields)] OR "compartment syndrome" (All Fields), we identified 45 studies. After screening all abstracts of these studies, 21 citations were identified reporting on CS after gynecologic surgeries [1, 2, 5, 10, 11, 16–18, 25–37]. Studies not reporting on CS or studies reporting on CS after non-gynecologic surgeries were excluded. Cross-reference searching identified a further 16 studies [3, 4, 6–9, 12–15, 20, 38–42]. Thus, in summary, 37 studies were selected for this review. Among the 37 studies, we found 29 case reports, five retrospective cohort studies, one survey, and one narrative review. One publication contained a case report and a retrospective cohort study. Figure 2 shows a diagram of the literature search. Table 1 shows the study characteristics and outcomes of patients with CS after gynecologic laparoscopy described in all 37 studies. The total number of women described in these 37 studies was 86. 46 of these women developed CS after open gynecologic surgery or without surgery and 40 of these women developed CS after gynecologic laparoscopy. The median duration of surgery was 5.4 (0.5–12) h. Most, but not all patients [49/86 (57%)], were placed in a dorsal lithotomy position during surgery. Fasciotomy with or without necrosectomy was the most common treatment, performed in 30/86 (35%) cases. The median CK and myoglobin serum levels among women with CS were 19,223 (177–27,412) U/L and 1248 (285–1360) µg/L, respectively. We identified two cases with a fatal outcome. However, in both cases, the fatal outcome was related to causes other than CS, namely liver cirrhosis and hemorrhage. Therefore, the mortality of CS in the literature was zero. However, the long-term morbidity among all reported cases was considerable with 14/86 (16%) women reporting permanent neurologic sequelae after CS.

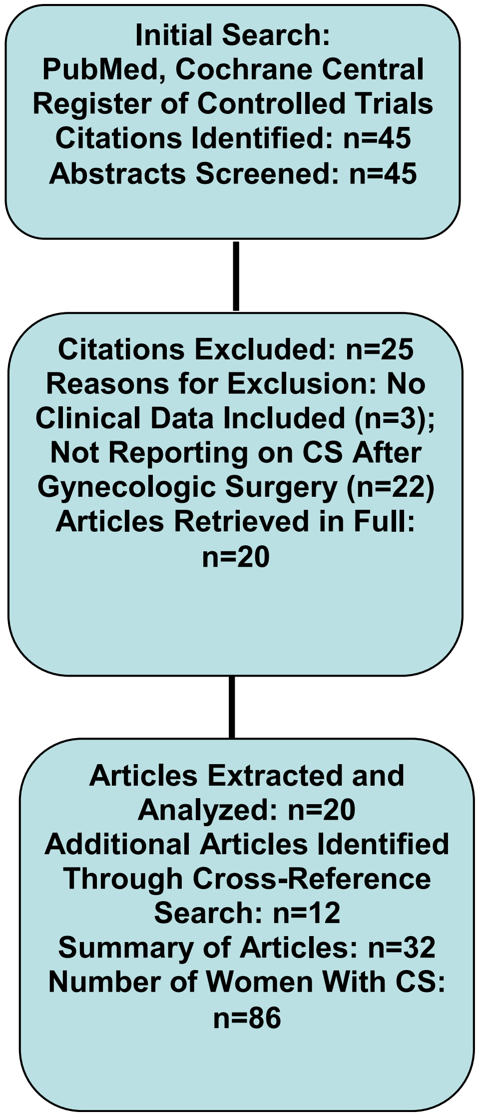

Fig. 2 Flow diagram of the literature search algorithm

Evaluation of serum CK and myoglobin

Characteristics of patients and performed surgeries are shown in Table 2. Median (range) duration of surgery was 56 (7–306) min. Duration of surgery was longer than 180 min in 34 patients (11.3%). Overall, median CK and myoglobin levels were 68 (14–1576) U/L and 45 (14–1040) µg/L, respectively. The 95th and 99th percentile of serum CK levels were 158 (142.8–202) U/L and 391.5 (259.3–2427.3) U/L, respectively. The 95th and 99th percentile of serum myoglobin levels were 152.3 (121.8–206.3) µg/L and 298.9 (213.4–1577.1) µg/L, respectively. In our series, the highest postoperative serum CK and myoglobin levels were 1576 U/L and 1040 µg/L, respectively, and were observed in a patient with metastasized malignant disease, followed by serum CK and myoglobin levels of 403 U/L and 300 µg/L, respectively, as the second highest serum levels in patients without developing CS. Clinical and serological parameters grouped according to duration of surgery< vs. ≥180 min are shown in Table 3. Serum myoglobin, but not CK, levels were significantly elevated in patients undergoing surgeries ≥180 min. Considering variables as continuous parameters, duration of surgery and patients' age were correlated with serum myoglobin, but not CK, levels in a univariate and multivariate analysis (Table 4).

Discussion

In a systematic review of the literature, we identified 86 women with CS after gynecologic surgery with 40 of these occurring after gynecologic laparoscopy. The median duration of surgery was 5.4 (0.5–12) h, and the median CK and myoglobin serum levels were 19,223 (177–27,412) U/L and 1248 (285–1360) µg/L, respectively. The long-term morbidity was considerable with 14/86 (16%) women reporting permanent neurologic sequelae. In addition, we have established normal postoperative serum levels of CK and myoglobin in a cohort study of women undergoing gynecologic laparoscopy.

A number of previously published papers are focusing on the reduction of complications in gynecologic surgery [43, 44]. Occurrence of CS is a very rare but devastating event in gynecologic surgery. Prevention strategies for a CS include minimization of operating time in lithotomy position, intermittent mobilization of legs during surgery, use of vacuum mattresses in order to prevent malposition of the patient during surgery, lowering the legs below the level of the right cardiac atrium, and intermittent compression devices [45]. Although the benefits of these interventions have not been proven in prospective, randomized trials, expert opinion suggests incorporating these procedures into daily clinical practice [45]. Furthermore, it has been stressed that gynecologists should be aware of this rare complication.

The diagnosis of a CS is notoriously difficult and can only be achieved by the invasive measurement of ICP. Predictive markers for the development of CS are warranted, because they would be less invasive and easily evaluable in clinical practice. Raising the suspicion of postoperative CS by means of a readily available, cheap, and noninvasive serum test could lead to a more rapid diagnosis and a better prognosis of affected patients, because the success of therapy, i.e., fasciotomy, is negatively associated with the elapsed time after surgery [1, 2].

Serum parameters are commonly used as predictive and prognostic parameters. Serum CK and myoglobin levels have been shown to be elevated in patients with CS. In our index patient, both serum parameters were markedly

Table 1 Patients' characteristics

Parameter	*n*	Time	*p* value	CK	*p* value	MB	*p* value
Total number of patients enrolled	300						
Number of surgeries with a surgery time ≥180 min	34						
Age							
<50 years	152	57 (7–273)	0.9	70 (14–392)	0.6	41 (14–243)	<0.001
50–60 years	76	54 (12–253)		68.5 (18–403)		48 (17–299)	
>70 years	72	53.5 (10–306)		67 (19–1576)		53 (20–1040)	
Body mass index							
No. of patients with body mass index <20	24	51.5 (9–226)	0.1	70.5 (19–1576)	0.1	51 (21–1040)	0.3
No. of patients with body mass index 20–25	122	49 (12–306)		70.5 (20–392)		43.5 (16–300)	
No. of patients with body mass index 25–30	92	60.5 (15–265)		59 (18–180)		44.5 (14–207)	
No. of patients with body mass index >30	62	66 (7–225)		77.5 (14–403)		49 (22–299)	
Types of laparoscopic surgeries							
Diagnostic laparoscopy including biopsies	27	25 (7–75)	<0.01	58 (18–157.6)	0.1	39 (14–1040)	0.004
Adnexal surgery	144	39 (12–100)		71.5 (20–403)		44 (16–226)	
Total laparoscopic hysterectomy for benign disease	46	92 (44–192)		72.5 (18–340)		45 (21–299)	
Laparoscopic sacrocolpopexy	18	94.5 (58–218)		62.5 (33–145)		39.5 (20–108)	
Laparoscopy for benign conditions miscellaneous	9	64 (29–131)		78 (42–149)		39 (21–153)	
Radical laparoscopic hysterectomy for malignant disease and lymphadenectomy	11	206 (185–273)		67 (14–91)		73 (28–215)	
Staging laparoscopy for malignant disease	24	117.5 (21–306)		53 (32–110)		46 (24–130)	
Total laparoscopic hysterectomy for malignant disease ± lymphadenectomy	21	181 (50–265)		67 (32–339)		61 (25–292)	

Values are given as absolute numbers, or medians (range), where appropriate

p-values were derived from ANOVA on ranks

Time duration of surgery, *CK* serum creatine kinase levels (U/L), *MB* serum myoglobin levels (µg/L)

elevated. Although normal values for serum CK and myoglobin levels are readily available, we have no data concerning postoperative normal values. It can reasonably be hypothesized that established normal values, i.e., preoperative values, cannot be used for postoperative prediction/exclusion of compartment syndrome.

Postoperative serum myoglobin, but not CK, levels were found to be correlated with duration of surgery and patients' age. In a multivariate analysis duration of surgery and patients' age were associated with serum myoglobin levels. In our series of 300 patients undergoing gynecologic laparoscopy, only one patient had serum CK and myoglobin levels greater than 1000 U/L or 1000 µg/L, respectively. Of note, this was a patient with metastasized malignant disease undergoing diagnostic laparoscopy. ICP values in this patient were normal. This observation suggests that the normal values established in our study may not apply to this category of patients.

Measurement of serum parameters indicative of CS might be especially valuable in patients who are not able to report pain, swelling, or other symptoms, because they are sedated or suffer from dementia. When measurement of serum CK and myoglobin levels is only performed in patients at "high risk" of CS, it can be hypothesized that only few patients will present with markedly elevated serum levels possibly making measurement of ICP necessary, whereas the risk of CS with "normal values" of CK and myoglobin seems low. Thus, we suggest to adopt a risk-based approach with the use of postoperative CK and myoglobin measurements only in patients after prolonged surgery or those with a combination of other risk factors such as intraoperative hypotension, hypovolemia, cardiovascular disease, and diabetes mellitus.

We have shown in a literature review that cases of CS are usually correlated with a marked increase in CK and myoglobin levels and have established upper limits of postoperative CK and myoglobin serum levels after gynecologic laparoscopy. Although it would not be prudent to recommend a general screening for CS after laparoscopy due to the rarity of the event, such measurements might be reasonable in patients at risk of CS. Markedly elevated CK and myoglobin serum levels should raise the suspicion of this devastating condition.

Table 2 Clinical studies describing women with compartment syndrome after gynecologic surgery

Author	Year	Study type	Number of CS cases (*n*)	Number of CS after LSC (*n*)	Indication (*n*)	Duration of surgery (h)	Lithotomy position (*n*)	Treatment (*n*)	CK serum levels (U/L)	MG serum levels (µg/L)	Mortality/permanent disability (*n*)
Adler [18]	1990	CR	1	0	Tubal anastomosis	–	1	–	–	–	–
Jacobs [37]	1992	CR	1	0	rHE	–	1	FASC	–	–	–
Schwartz [17]	1993	CR	1	0	Neovagina	–	1	–	–	–	–
Honda [16]	1995	CR	1	1	HE	2.5	1	FASC	–	–	0/0
Kemp [39]	1996	CR	1	0	rHE	7	1	FASC	–	–	0/0
Von Gruenigen [15]	1999	CR	2	0	HE	–	0	LAP	–	–	1[b]/0
Tonnies [41]	1999	CR	2	0	–	–	2	–	–	–	–
Jyothi [38]	2000	CR	1	0	Delivery	4	1	FASC	–	–	0/0
Raatz [36]	2001	RCS	3	3	rHE	6.3	3	CT	–	–	–
Cohen [14]	2001	CR	1	0	VVF	5.7	1	FASC	–	285	0/0
Wassenaar [20]	2006	RCS	1	0	Neovagina	6.5	1	FASC	15,424	1360	0/1
Yanazume [13]	2006	CR	1	1	rHE	6	1	Conservative	9843	652	0/1
Kendrick [35]	2006	CR	1	0	Delivery	–	0	LAP	–	–	0/0
Khen-Dunlop [33]	2007	RCS	1	0	Vaginoplasty	4.5	1	FASC	–	–	0/0
Byers [34]	2007	CR	1	0	Cervical pregnancy	–	–	FASC	–	–	0/1
Soltsman [11]	2008	CR	1	1	EP	–	1	Paracentesis	–	–	0/0
Olah [12]	2008	CR	1	0	TOT	–	1	Antibiotics	–	–	0/0
Otsuka [32]	2008	RCS	1	1	VVF	6.5	–	–	–	–	0/0
Tomassetti [9]	2009	CR, RCS	4	4	END	4.8	4	FASC (1), (3)	–	–	0/1
Tsutsui [31]	2009	CR	1	–	rHE	–	–	FASC	20,000	–	0/0
Szalay [40]	2009	CR	2	2	OC, END	5.8	2	FASC (2)	–	–	0/0
Roman [8]	2010	RCS	2	2	END	–	–	–	–	–	0/–
Deras [29]	2010	CR	1	1	END	12	1	FASC	–	–	0/1
Lee [30]	2010	CR	1	0	Hysteroscopy	2.2	1	LSC	–	–	0/0
Ulrich [42]	2010	CR	1	0	OC	6	0	FASC	10,552	2696	0/1
Radosa [7]	2011	CR	1	0	C-section	0.5	0	FASC	–	–	0/0

Table 2 continued

Author	Year	Study type	Number of CS cases (*n*)	Number of CS after LSC (*n*)	Indication (*n*)	Duration of surgery (h)	Lithotomy position (*n*)	Treatment (*n*)	CK serum levels (U/L)	MG serum levels (µg/L)	Mortality/ permanent disability (*n*)
Nakamura [10]	2011	CR	1	0	rHE	6	0	FASC	27,412	–	0/0
Sanda [26]	2011	CR	1	0	EP	–	–	LAP	–	–	1[a]/–
Lawrenz [28]	2011	CR	1	1	rHE	4	1	–	–	–	0/0
Na [25]	2012	CR	2	0	Delivery	–	0	LAP (2)	–	–	0/0
Zavras [27]	2012	CR	1	0	OC	–	–	LAP	–	–	0/0
Veisi [3]	2013	CR	1	0	OHSS	–	–	LAP	–	–	0/0
Boesgaard-Kjer [6]	2013	CR	2	2	MYO; END	5; 5	2	FASC;	14,395; 14,000	–	0/2
Bauer [1]	2014	RVW	19	7	rHE (1), OC (1), END (3), MYO (2)	5.8	7	–	–	–	0/0
Bauer [2]	2014	SUR	21	12	HE (2), MYO (1), PEL (1), (7)	5.2	12	FASC (12)			0/6
Chikazawa [4]	2016	CR	1	1	rHE	5.9	1	Conservative	177	–	0/–
Stornelli [5]	2016	CR	1	1	EP	1.5	1	FASC	22,760	–	0/0
Pooled analysis	–	–	86	40	–	5.4 (0.5–12)	49/86 (57%)	FASC 30/86 (35%)	19,223 (177–27,412)	1248 (285–1360)	2/14

RVW review, *n* number of cases, *rHE* radical hysterectomy, *END* endometriosis resection, *MYO* myomectomy, *CK* creatine kinase, *MG* myoglobin, *EP* ectopic pregnancy, *FASC* fasciotomy, *SUR* survey, *PEL* pelvic lymphadenectomy, *CR* case report, *VVF* vesicovaginal fistula repair, *RCS* retrospective cohort study, *LAP* laparotomy, *CT* conservative treatment, *C-section* cesarean section, *TOT* trans-obturator tape, *OHSS* ovarian hyperstimulation syndrome

[a] Fatality due to hemorrhagic shock

[b] Fatality due to complications related to liver cirrhosis

Table 3 Serum creatine kinase and myoglobin levels broken down by duration of surgery <180 vs. ≥180 min

	Duration of surgery <180 min	Duration of surgery ≥180 min	p^a
Patients' age (years)	48.9 (15.5–86.5)	55.8 (30.1–84.3)	0.03
Body mass index	25.1 (14.9–48.4)	25.7 (18–40.3)	0.3
Serum creatine kinase levels (U/L)	69.5 (18–1576)	64 (14–339)	0.7
Serum myoglobin levels (µg/L)	43 (14–1040)	73 (28–292)	<0.001

Values are medians (range)

[a] Mann–Whitney *U* test

Table 4 Univariate and multivariate correlation between clinical parameters with serum creatine kinase and myoglobin levels

	Serum creatine kinase levels		Serum myoglobin levels	
	Univariable analysis†	Multivariable analysis‡	Univariable analysis†	Multivariable analysis‡
Patients' age	0.2	0.7	0.008	0.02
Body mass index	0.9	0.8	0.4	0.9
Duration of surgery	0.6	0.4	0.005	0.03

p values are given for † Pearson's correlation coefficient, ‡ multivariate Cox regression model

Author contributions KH-F involved in protocol/project development, data collection and management, data analysis, and manuscript writing/editing. JL contributed to protocol/project development, data collection and management, and manuscript writing/editing. GB-P performed data collection and management and manuscript writing/editing. FR participated in protocol/project development and manuscript writing/editing. VU involved in data collection and management, data analysis, and manuscript writing/editing. LH and CT performed protocol/project development, data analysis, and manuscript writing/editing.

Compliance with ethical standards

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Conflict of interest All authors have no actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations within two years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

IRB approval IRB approval was obtained for the present study.

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