

Evidence-Based Anesthesia for Major Gynecologic Surgery



Jeanette R. Bauchat, MD^a,
Ashraf S. Habib, MBBCh, MSc, MHSc, FRCA^{b,*}

KEYWORDS

• Enhanced recovery • ERAS • Gynecologic surgery • Fast track

KEY POINTS

- Studies on enhanced recovery after major gynecologic surgery are limited but seem to have similar outcome benefits to populations who have had colorectal surgery.
- Effective regional anesthetic techniques used in gynecologic surgery include spinal anesthesia, epidural analgesia, transversus abdominis plane blocks, local anesthetic wound infusions, and intraperitoneal instillation catheters.
- Effective nonopioid analgesics known to reduce opioid consumption after gynecologic surgery include pregabalin, gabapentin, nonsteroidal antiinflammatory drugs, cyclooxygenase 2 inhibitors, and paracetamol.
- A multimodal antiemetic strategy to reduce the baseline risk of postoperative nausea and vomiting in conjunction with combination antiemetic therapy is imperative in this high-risk population.
- Randomized controlled trials of the ideal fluid management strategies in this surgical population are needed.

INTRODUCTION

The last 2 decades have seen significant changes in the surgical approach to gynecologic surgery. Minimally invasive surgeries have been more commonly performed and have been associated with comparable long-term outcomes compared with open surgery.¹ Although operative time is longer with minimally invasive surgery, hospital stay is significantly shorter, and analgesic and antiemetic needs are significantly reduced compared with open surgery.^{1,2} However, there has been little attention to optimizing other surgical and anesthetic elements of the perioperative care of these patients.

The authors have no conflicts of interest.

^a Northwestern University, Feinberg School of Medicine, 250 East Huron Street, F5-704, Chicago, IL 60611, USA; ^b Duke University Medical Center, Box 3094, Durham, NC 27710, USA

* Corresponding author.

E-mail address: ashraf.habib@duke.edu

Anesthesiology Clin 33 (2015) 173–207
<http://dx.doi.org/10.1016/j.anclin.2014.11.011>

anesthesiology.theclinics.com

1932-2275/15/\$ – see front matter © 2015 Elsevier Inc. All rights reserved.

The concepts and practices of enhanced recovery after surgery (ERAS) are well established for colorectal surgery but until recently have not been applied to gynecologic surgery. High-quality meta-analyses have shown the effectiveness of ERAS principles in reducing hospital length of stay and overall complications but not necessarily surgical complications.^{3,4} Studies that assess fast-tracking or enhanced recovery after major gynecologic surgery typically apply the ERAS guidelines derived from colorectal surgery, because there are no specific guidelines for enhanced recovery after major gynecologic surgery. In this article, major gynecologic surgery refers to the surgeries listed in **Box 1**.

Some general concepts of the ERAS protocol apply to all surgical patient populations (**Box 2**).⁵ The means by which individual components of the ERAS protocol are achieved may differ, depending on the patient population and type of surgery. For example, unlike colorectal surgery, gynecologic surgery patients are all women. It is well established that women differ significantly from men from a pharmacokinetic and pharmacodynamic standpoint, which may influence the optimal anesthetic drug choice and antiemetic or analgesic strategies in ERAS protocols for gynecologic surgery compared with colorectal surgeries.⁶

This article focuses on meta-analyses, randomized controlled trials (RCTs), and large prospective impact studies conducted in the gynecologic surgery population investigating aspects of the ERAS protocol over which anesthesiologists exercise the most influence. The best evidence is presented for 4 specific aspects of the ERAS protocol: anesthetic choice, nonopioid multimodal pain management, postoperative nausea and vomiting (PONV) prevention strategies, and fluid management. This article concludes with the general ERAS principles applied to this specific patient population, because anesthesiologists should be aware of all the ERAS interventions as we become leaders of the perioperative surgical home.

ENHANCED RECOVERY AFTER MAJOR GYNECOLOGIC SURGERY

The first descriptive study exploring ERAS principles in major gynecologic surgery was conducted 10 years ago.⁷ The benefits of implementation of ERAS principles in the gynecologic surgery population were explored in 1 RCT,⁸ but mostly in preintervention and postintervention studies. Studies assessing impact of ERAS protocol implementation on outcomes for major gynecologic surgeries are summarized in **Table 1**. All of those studies reported a reduction in the duration of hospital stay, in addition to other

Box 1

Major gynecologic surgeries included in this article

Laparotomy for malignant gynecologic cancers

Hysterectomy, lymphadenectomy, omentectomy

Complex cytoreductive surgery

Urogynecologic pelvic organ prolapse surgery

Total or partial abdominal hysterectomy

Vaginal hysterectomy

Abdominal myomectomy

Salpingo-oophorectomy

Ovarian cystectomy

Box 2**Common aspects to all ERAS protocols**

- Preoperative care
 - Optimize preoperative care for specific diseases (eg, adjusting insulin or antihypertensive medications before surgery)
 - Preoperative counseling
- Intraoperative care
 - Optimizing prophylactic antibiotic administration
 - Use of regional anesthesia intraoperatively
 - Use of minimally invasive surgery when feasible
 - Maintenance of intraoperative normothermia
 - Optimize fluid management
 - Nausea and vomiting prophylaxis
 - Optimize oxygen delivery
- Postoperative care
 - Optimize sleep
 - Ileus prevention (ie, early feeding, avoid nasogastric tube, early mobilization)
 - Minimize drains, tubes, and catheters
 - Opioid-sparing multimodal pain management
 - Continue home medications
 - Postoperative discharge planning
 - Thromboembolic prophylaxis (ie, pneumatic compression devices, anticoagulation)

improvements. However, there was tremendous variation in the ERAS interventions used and how each intervention was standardized. For instance, few studies attempted to standardize intraoperative anesthetic technique.^{8–11} The opioid-sparing analgesic protocol varied from no standardization,¹² to nerve blocks,¹³ multimodal nonopioid oral analgesics,⁹ or different neuraxial analgesic techniques.^{8–11} Administration of prophylactic antiemetics was standardized in 5 of those 8 studies, but they differed markedly in the type and number of agents used.^{8,9,11,13,14} Intraoperative fluid administration was clearly standardized in only 1 study.⁸

REGIONAL ANESTHETIC TECHNIQUES FOR ENHANCED RECOVERY AFTER MAJOR GYNECOLOGIC SURGERY

Opioid-sparing analgesic regimens are believed to be an integral part of an ERAS protocol, because opioids have been implicated in immunosuppression, postoperative hyperalgesia, PONV, paralytic ileus, and delay of early mobilization as a result of sedation.^{15–17} A variety of regional techniques, including neuraxial and peripheral nerve blocks may be used to provide postoperative analgesia, reducing opioid consumption and blunting the surgical stress response.¹⁸

There are no RCTs delineating the ideal intraoperative anesthetic protocol to support ERAS principles, even in guidelines already established for colorectal surgery. Nonetheless, intraoperative neuraxial anesthesia has been implemented in multiple

Table 1
Summary of studies using enhanced recovery principles for major gynecologic surgeries

Reference, Surgery Type	Study Type	Number of Patients	Implemented ERAS Interventions		Summary of ERAS Outcomes
Kroon et al, ⁸ 2010 Abdominal hysterectomy	RCT	Control (N = 26) ERAS (N = 27)	Control Preoperative: Paracetamol and NSAID or COX-2 inhibitor Intraoperative: General anesthesia N ₂ O + volatile agent PONV prophylaxis ondansetron Postoperative: Paracetamol + morphine PCA	ERAS Protocol Preoperative: Carbohydrate drink ≤2 h before surgery Paracetamol and NSAID or COX 2 inhibitor Intraoperative: Spinal anesthesia bupivacaine + morphine 100 µg PONV prophylaxis betamethasone + droperidol + ondansetron IV fluid restricted 500 mL/h Postoperative: IV fluids stopped with oral intake Paracetamol + NSAID	Shorter recovery room length of stay (median 180 vs 237 min) Lower rate of PONV on day 1 (11% vs 50%) Shorter time to oral intake (median 4 vs 5 h) Shorter duration of indwelling urinary catheter (median 9 vs 22 h) Reduced length of hospital stay (median 2 vs 3 d)
DeGroot et al, ¹³⁵ 2014 Gynecologic cancer surgery	Nonrandomized prospective pre and post intervention	Pre (N = 38) Post (N = 77)	Preoperative: Counseling (not specified) Carbohydrate drink Avoidance of bowel preparations Intraoperative: Avoidance of long-acting anesthetic (not specified) Avoidance of opioids Thoracic epidural analgesia Avoidance of NG tubes Postoperative: Oral fluids day of surgery Normal diet POD 1 Early mobilization >3 times POD 1		Reduced length of hospital stay (median 5 vs 7 d) Increased rate of early feeding (oral fluids on POD 0 increased from 0% to 94%; normal diet on POD 1 increased from 0% to 58%) Reduced time to functional recovery ^a (median 3 d vs 6 d)

<p>Kalogera et al,⁹ 2013 Laparotomy gynecologic cancer surgery Urogynecologic organ prolapse surgery</p>	<p>Retrospective cohort pre and post intervention</p>	<p>Pre (N = 235) Post (N = 241)</p>	<p>Preoperative: Carbohydrate loading drink Fluids \leq4 h before surgery No bowel preparation Preoperative acetaminophen, COX-2 inhibitor, or gabapentin Intraoperative: Triple-agent antiemetic prophylaxis Minimize crystalloid, administer colloid if needed <i>Laparotomy analgesic medications:</i> Ketorolac or ketamine LA wound infiltration <i>Pelvic organ prolapse analgesic medications:</i> Spinal anesthesia + hydromorphone Ketorolac Postoperative: Postoperative fluids 40 mL/h X 24 h or until oral intake Early food intake POD 0 + nutritional supplement Early mobilization (out of bed night of surgery) Scheduled nonopioid analgesics: ketorolac or tramadol, paracetamol, oral hydromorphone as needed</p>	<p>Lower fluid administration (1 L less with no intraoperative hypotension) Reduced opioid usage (80% reduction over 48 h) Higher PONV rate (nausea 55.6% vs 38.5%; vomiting 17.3% vs 2.6%) Faster return of bowel function (1 d earlier) Reduced hospital length of stay by 4 d Cost savings (\$7600 per patient) High patient satisfaction</p>
---	---	---	---	--

(continued on next page)

Table 1
(continued)

Reference, Surgery Type	Study Type	Number of Patients	Implemented ERAS Interventions	Summary of ERAS Outcomes
Wijk et al, ¹⁴ 2014 Abdominal hysterectomy ^b	Retrospective pre and post intervention	Pre (N = 120) Post (N = 85)	<p>Preoperative:</p> <ul style="list-style-type: none"> Counseling regarding ERAS protocol Malnourished patients given nutritional supplement Carbohydrate drink 2 h before surgery Preoperative paracetamol Preoperative oral antibiotic <p>Intraoperative:</p> <ul style="list-style-type: none"> Maintain normothermia with forced air and warm IV fluids Standard antiemetic regimen: droperidol, dexamethasone, in addition, for high-risk patients, rescue treatment with ondansetron then metoclopramide <p>Postoperative:</p> <ul style="list-style-type: none"> Standardized nonopioid analgesics: scheduled diclofenac and paracetamol IV fluids stopped with oral intake, normal diet 2 h after surgery Early mobilization (2 h after surgery) Routine thromboprophylaxis Clear discharge criteria (eat normally, independent mobilization, oral analgesics, no bowel obstruction) 	<p>Rate of target length of stay (2 d) increased (53% vs 73%)</p> <p>Target length of stay correlated with increasing number of ERAS protocol parameter compliance</p> <p>Reduced hospital length of stay (median 2.6 vs 2.3 d)</p>
Sjetne et al, ¹² 2014 Abdominal hysterectomy ^b Urogynecologic organ prolapse surgery	Nonrandomized prospective pre, immediately post, and 1 y post intervention	Pre (N = 35) Post (N = 45) 1 y Post (N = 45)	<p>Preoperative:</p> <ul style="list-style-type: none"> Counseling regarding ERAS protocol <p>Intraoperative:</p> <ul style="list-style-type: none"> None specified <p>Postoperative:</p> <ul style="list-style-type: none"> IV and urinary catheter removed in recovery room Normal diet within hours (not specified) after surgery Stopped routine postoperative enemas Mobilization within hours after surgery Oral analgesics started immediately 	<p>Reduced hospital length of stay (median days pre 4.7, post 3.4, 1 y post 3.4)</p> <p>Reduced nursing workload (patient contact minutes Pre 86 min, post 70.9 min, 1 y post 72.7 min)</p>

Yoong et al, ¹³ 2014 Vaginal hysterectomy	Retrospective case-matched pre and post intervention	Pre (N = 50) Post (N = 50)	<p>Preoperative:</p> <ul style="list-style-type: none"> Family support assessment Counseling regarding surgery (1 h audiovisual session/ discussion) <p>Intraoperative:</p> <ul style="list-style-type: none"> Surgical approach: avoid laparoscopy or abdominal incisions Regional anesthesia with pudendal and uterosacral nerve blocks Maintain intraoperative normothermia >36° Standardized antiemetic protocol: dexamethasone + ondansetron, rescue agent cyclizine <p>Postoperative:</p> <ul style="list-style-type: none"> No routine vaginal packing No routine urinary catheter Early feeding Early mobilization Hired RN discharge planner Standardized assessment algorithm to evaluate discharge readiness 	<ul style="list-style-type: none"> Reduced hospital length of stay (median 22 h vs 45.5 h) Increase number of women discharged in <24 h (78% vs 15.6%) Reduced rate of vaginal packing (82.2% vs 52%) Reduced rate of urinary catheter use (96% vs 84.4%) Cost savings (\$159.45 per patient)
Dickson et al, ¹⁰ 2012 Abdominal hysterectomy ^c	Retrospective case-matched pre and post intervention	Pre (N = 100) Post (N = 100)	<p>Preoperative:</p> <ul style="list-style-type: none"> Counseling regarding ERAS protocol <p>Intraoperative:</p> <ul style="list-style-type: none"> Spinal anesthesia with intrathecal morphine (60–100 µg) <p>Postoperative:</p> <ul style="list-style-type: none"> Early mobilization (day of surgery) Normal diet (day of surgery) 	<ul style="list-style-type: none"> Increased use of spinal anesthesia (5% vs 83%) Reduced length of hospital stay (median 3 d vs 1 d)

(continued on next page)

Table 1
(continued)

Reference, Surgery Type	Study Type	Number of Patients	Implemented ERAS Interventions	Summary of ERAS Outcomes
Marx et al, ¹¹ 2006 Laparotomy gynecologic cancer surgery	Retrospective pre and post intervention	Pre (N = 72) Post (N = 69)	Preoperative: No premedication Preoperative paracetamol No bowel preparation Thromboprophylaxis Intraoperative: Routine use of epidural anesthesia Antiemetic prophylaxis (dexamethasone + ondansetron) Routine antibiotic prophylaxis Postoperative: Routine use of epidural analgesia Food and nutritional supplements 4 h after surgery Magnesia (promotility agents) Early mobilization day or surgery and standardized mobilization Schedule to remove urinary and epidural catheter	Reduced hospital length of stay (median 6 d vs 5 d) Reduced severe complications (12.5% vs 1.4%)

Abbreviations: IV, intravenous; LA, local anesthetic; NG, nasogastric; NSAID, nonsteroidal antiinflammatory drug; PCA, patient controlled analgesia; POD, postoperative day; RN, registered nurse.

^a Functional recovery score is based on: resumption of normal oral and food intake, independent mobilization, and pain controlled on oral analgesics.

^b Malignant and benign indication.

^c Benign indication.

Data from Refs.^{8-14,135}

fast-track protocols because of proven benefits on attenuating the physiologic surgical stress response and showing opioid-sparing effects.¹⁸ **Table 2**^{18–28} summarizes the potential benefits of neuraxial anesthesia on ERAS protocol goals, as shown by several meta-analyses and RCTs. Despite the known benefits of regional anesthesia, there are few RCTs comparing general anesthesia alone with either regional anesthesia alone or a combination of general anesthesia with regional anesthesia in major gynecologic surgery.

Spinal Anesthesia

Most studies using regional anesthesia as a sole anesthetic are conducted in open abdominal hysterectomies or pelvic organ prolapse surgery under spinal anesthesia. **Table 3**^{29–33} summarizes the RCTs that compare regional anesthesia as a sole technique or in combination with general anesthesia with general anesthesia alone on ERAS outcomes. Most of these studies show a clear benefit of spinal anesthesia compared with general anesthesia for reducing postoperative opioid consumption, likely because of the addition of intrathecal morphine to the spinal injectate.^{29,30,32,33} Spinal anesthesia also seems to be more cost effective, in part because of shorter recovery room length of stays.^{31,32} The effect of spinal anesthesia on hospital length of stay was mixed,^{29,32} but the evidence favors spinal anesthesia for hysterectomies to enhance recovery in the immediate postoperative period.

Combined General and Epidural Anesthesia

Epidural anesthesia and analgesia is typically used as an adjuvant to general anesthesia and as a primary modality for postoperative pain management in hysterectomies and laparotomies for complex gynecologic cancer surgeries. There are few RCTs examining the impact of epidural analgesia on ERAS principles in this population. **Table 4**^{34–38} summarizes RCTs comparing epidural analgesia for intraoperative

ERAS Principle	Positive Impact of Regional Anesthesia
Attenuation of physiologic surgical stress response	Reduced endocrine and metabolic response to surgery ¹⁸ Thoracic epidurals reduced the incidence of myocardial infarction ¹⁹
Reduction of inflammation	Reduced inflammatory markers ²⁰
Maintenance of normothermia	Inhibits physiologic demand of shivering ²¹
Nausea and vomiting prophylaxis	Less nausea and vomiting than opioids if local anesthetics are used alone ²²
Optimization of oxygen delivery	Improve oxygen delivery ²³ Reduced pulmonary complications ²⁴
Opioid-sparing multimodal pain management	Reduces opioid consumption ²⁵ Excellent analgesia ^{22,26} Reduce chronic pain ²⁷
Optimization of sleep	Excellent analgesia ^{22,26}
Ileus prevention/early feeding	Promote gastric motility ²²
Early mobilization	Thoracic epidural can promote early mobilization as a result of excellent pain control ²²
Thromboembolic prophylaxis	Reduced deep vein thrombosis and pulmonary embolism ³²

Table 3
Summary of RCTs showing the impact of spinal anesthesia on ERAS outcomes

Type of Surgery	Study	Anesthetic Technique (Number of Patients)	Anesthetic Medication Administered	Other ERAS Interventions	ERAS Outcomes
Vaginal hysterectomy ^a ± urogynecologic pelvic organ prolapse surgery	Sprung et al, ²⁹ 2006	Spinal anesthesia (N = 45) General anesthesia (N = 44)	IT: bupivacaine + clonidine + morphine (≤200 µg) S: midazolam + propofol I: thiopental + fentanyl M: isoflurane + N ₂ O + morphine	Ketorolac 30 mg once	Favors spinal: Reduced morphine request rate in recovery room (70% vs 11%) Reduced morphine use in first 12 h (median 7.9 vs 14.8 mg) More patients with no pain at postoperative wk 2 (69% vs 48%) No difference: Request for antiemetic medications Hospital length of stay Functional status at 12 wk ^b
Abdominal hysterectomy ^a	Castro-Alves et al, ³⁰ 2011	Spinal anesthesia (N = 34) General anesthesia (N = 34)	IT: Bupivacaine + fentanyl + morphine (60 µg) S: Midazolam I: propofol + fentanyl M: isoflurane + fentanyl	Scheduled ketoprofen and metamizole Standardized antiemetic regimen (dexamethasone + ondansetron, rescue: metoclopramide)	Favors spinal: Higher quality of recovery scores at 24 h ^c (median difference of 17) Lower pain scores at rest and coughing at 24 h (4 vs 0 and 5 vs 2, respectively) Reduced morphine use in PACU (6 vs 0 mg) Reduced incidence of nausea (32% vs 12%)
Abdominal hysterectomy ^a	Borendal Wodlin et al, ³¹ 2011	Spinal anesthesia (N = 82) General anesthesia (N = 80)	IT: bupivacaine + morphine (200 µg) I and M: propofol + fentanyl	Counseling regarding surgical procedure Preoperative paracetamol Postoperative scheduled paracetamol and NSAID (not specified) Early mobilization Early feeding	Favors spinal: More cost-effective (\$969 savings per patient) Shorter recovery room length of stay (median 282 vs 234 min) Improved HRQoL scores ^d

Abdominal hysterectomy ^e	Massicotte et al, ³² 2009	Spinal anesthesia (N = 20) General anesthesia (N = 20)	IT: bupivacaine + fentanyl + morphine (150 µg) S: midazolam I: propofol + sufentanil M: desflurane + sufentanil	No premedication Postoperative scheduled indomethacin	Favors spinal: Reduced morphine use in first 48 h (median 19 vs 81 mg) Shorter recovery room length of stay (median 52 vs 73 min) Lower pain scores until the eighteenth hour (~30–50 lower VAS on a 100 VAS scale) Shorter hospital length of stay (median 2.2 vs 3.3 d) No difference: Nausea/vomiting
Abdominal hysterectomy ^a	Vaida et al, ³³ 2000	Spinal and general anesthesia (N = 15) General anesthesia (N = 15)	IT: bupivacaine I: midazolam M: isoflurane + N ₂ O I: midazolam M: isoflurane + N ₂ O	None	Favors spinal: Longer time to first request of analgesia (median 48 vs 9 min) Reduced opioid use in recovery room and from 2–24 h (median 32 vs 40.5 mg)

Abbreviations: HRQoL, health-related quality of life; I, induction; IT, intrathecal; M, maintenance; N₂O, nitrous oxide; PACU, postanesthesia care unit; S, sedation; VAS, visual analog scale.

^a Benign indication.

^b Functional status as measured by the validated Short Form 36 health survey, which includes patient-perceived physical and social functioning, physical and emotional activity limitations, mental health, vitality, and general health assessment.

^c Quality of recovery (QoR) score QoR-40 assesses physical comfort, physical independence, emotional state, psychological support, and pain. A 10-point difference in score reflects a 15% improvement in QoR.

^d HRQoL assesses mobility, self-care, ability to undertake usual activities, pain/discomfort, anxiety/depression. A score of 0 indicates death, 1 indicates full health.

^e Malignant and benign indication.

Data from Refs.^{29–33}

Table 4
Summary of RCTs showing the impact of epidural anesthesia on ERAS outcomes

Type of Surgery	Study	Anesthetic Technique (Number of Patients)	Anesthetic Medication Administered	Other ERAS Interventions	ERAS Outcomes
Gynecologic cancer surgery	Ferguson et al, ³⁴ 2009	Preincision epidural anesthesia + general anesthesia (N = 67) General anesthesia (N = 68)	PreE: bupivacaine + morphine for 24 h I and M: not specified I and M: not specified	Scheduled ketorolac for 48 h Early mobilization POD 1 Early feeding POD 1 Thromboembolic prophylaxis	Favors epidural: Lower mean pain scores at rest POD 1 (VAS 3.3 vs 4.3) Lower mean pain scores at rest on POD 2, 3, 4 (VAS 5.5, 5.0, 4.7 vs 6.7, 5.5, 5.7, respectively) Higher patient satisfaction No difference: Combined postoperative complications Nausea/vomiting Hospital length of stay
Major gynecologic surgery ^a	Katz et al, ³⁵ 2003	Preincision epidural anesthesia + general anesthesia (N = 45) Postincision epidural injection + general anesthesia (N = 49) Sham epidural + general anesthesia (N = 47)	PreE: lidocaine + epinephrine + fentanyl 1 dose PostE: saline I: thiopental M: N ₂ O + isoflurane PreE: saline PostE: lidocaine + epinephrine + fentanyl 1 dose I: thiopental M: N ₂ O + isofluran PreE: saline PostE: saline I: thiopental + fentanyl M: N ₂ O + isoflurane	None specified	Favors preincision then postincision epidural over control: Cumulative 24 h morphine use lowest in preincision epidural (preE 57 mg vs postE 59 mg vs control 72 mg) Cumulative 48 h morphine use lowest in preincision epidural (preE 90 mg vs postE 95 mg vs control 113 mg)

Abdominal hysterectomy ^b	Jorgensen et al, ³⁶ 2001	Preincision epidural injection + general anesthesia (N = 20) Postincision epidural injection + general anesthesia (N = 20) General anesthesia (N = 20)	PreE: lidocaine PostE: bupivacaine for 24 h I and M: see below PreE: saline PostE: bupivacaine for 24 h I and M: see below I: propofol + alfentanil + fentanyl M: propofol + fentanyl	Scheduled paracetamol for 48 h and ketorolac for 72 h Early feeding Discharge planning	Favor preincision epidural (no differences between postE or control groups): Reduced pain scores during rest, coughing and movement for 24 h (VAS lower by 30 than other 2 groups) Reduced requests for morphine (60%–70% fewer requests than other 2 groups) Shorter time to first flatus No difference: Nausea/vomiting Time to first defecation Readiness for discharge
Abdominal hysterectomy ^b	Chinachoti et al, ³⁷ 2002	Preincision and postincision epidural + general anesthesia Preincision epidural + general anesthesia	PreE: ropivacaine PostE: ropivacaine for 24 h PreE: ropivacaine PostE: saline for 24 h	Ketorolac for 24 h	Favors continuing postoperative epidural: Lower pain scores at rest (difference of ~30 VAS, AUCM pain difference –11) Lower pain scores during coughing (difference of ~30 VAS, AUCM pain difference –11) Equivalent: Time to first mobilization

(continued on next page)

Table 4
(continued)

Type of Surgery	Study	Anesthetic Technique (Number of Patients)	Anesthetic Medication Administered	Other ERAS Interventions	ERAS Outcomes
Abdominal hysterectomy ^c	Wattwil et al, ³⁸ 1989	Preincision epidural + general anesthesia (N = 20)	PreE: bupivacaine for 26–30 h I: thiopental M: isoflurane + N ₂ O	None specified	Favors epidural: Reduced pain scores (VAS mean 1.9 vs 4.4) Shorter time to first flatus (mean 31 vs 58 h) Shorter time to first defecation (mean 70 vs 103 h) Lower postoperative blood glucose at 3, 6, 9 h No difference: Hospital length of stay
		General anesthesia (N = 20)	I: thiopental M: isoflurane + N ₂ O		

Abbreviations: AUCM, area under the curve measurement; I, induction; M, maintenance; N₂O, nitrous oxide; POD, postoperative day; PostE, epidural injection after incision or procedure; PreE, epidural injection before incision; VAS, visual analog scale.

^a Abdominal hysterectomy (malignant and benign indication, midline and horizontal incisions), myomectomy, salpingo-oophorectomy, ovarian cystectomy.

^b Indication not specified.

^c Malignant and benign indication.

Data from Refs.^{34–38}

and postoperative pain management with an opioid-based analgesic regimen alone after general anesthesia. Overall, these studies confirm the superiority of epidural analgesia compared with patient-controlled opioid analgesia for postoperative pain management after major gynecologic surgery.^{34–38} Two studies reported improved gastrointestinal function.^{36,38} However, none of these studies reported that epidurals could shorten the hospital length of stay despite improved pain control, reduced opioid consumption, and faster return of gastrointestinal function.^{34,36,38} This finding highlights the importance of incorporating other ERAS principles to optimize patient outcomes.

Impact of epidural infusion medications on outcomes with epidural analgesia

A Cochrane database review including 22 studies²² concluded that epidural analgesia promotes faster return of bowel function compared with intravenous (IV) opioids, but there were not enough studies to ascertain whether epidural local anesthetic alone promotes faster return of bowel compared with epidural local anesthetic with opioid. Two RCTs^{39,40} reported slower uptake of paracetamol (an indirect measure of gastric motility) in volunteers and patients receiving epidural morphine or fentanyl, with no effect on gastric motility in those receiving local anesthetic alone. In 1 RCT in major gynecologic surgery,⁴¹ the incidence of PONV was lower and the hospital length of stay shorter with epidural bupivacaine + fentanyl compared with epidural bupivacaine + morphine, with no difference in return of bowel function. Four studies in the gynecologic surgery population^{36,38,42,43} reported faster return of bowel function in patients receiving epidural local anesthetic alone compared with a combination of local anesthetic with opioids. Although the meta-analysis²² reported that a combination of local anesthetic and opioid provides better postoperative pain control than local anesthetic alone, both groups had very low postoperative pain scores, and it may be beneficial to avoid epidural opioids (morphine in particular) to promote faster return of bowel function and add them into the epidural solution only if there is inadequate analgesia.

Impact of epidural anesthesia on survival in gynecologic cancer surgery

Retrospective and nonrandomized prospective trials report conflicting evidence of beneficial^{44–47} or detrimental effect^{48,49} of epidural analgesia with regards to tumor spread and survival in gynecologic oncology surgeries. Most retrospective trials,^{50–52} but not all,⁵³ report possible survival benefit in women receiving epidural analgesia for gynecologic malignancies. Some studies^{15,54} suggest that epidurals may inhibit tumor spread and growth because of intrinsic tumor suppression properties of local anesthetics and minimizing opioid-induced and surgically induced immunosuppression. On the other hand, an RCT in women undergoing surgery for ovarian cancer⁵⁵ reported that patients receiving combined epidural and general anesthesia showed higher antitumorigenic cytokines and natural killer cell cytotoxicity than women receiving general anesthesia alone.

Other Regional Anesthetic Techniques Combined with General Anesthesia

Transversus abdominis plane block

Transversus abdominis plane (TAP) block can be used for Pfannenstiel or midline incisions. A meta-analysis of 5 studies⁵⁶ reported reduction in 24-hour pain scores and opioid consumption (reduced morphine equivalents by 5–19 mg) in patients who received a TAP block compared with no block for major open gynecologic surgery. In a meta-analysis of 10 studies in all-type laparoscopic surgery,⁵⁷ 3 of which were gynecologic, TAP blocks were shown to be effective in reducing postoperative pain scores and opioid consumption, particularly when administered preoperatively. The TAP block has shown conflicting data with regard to improvement in quality of

recovery scores or opioid consumption after laparoscopic gynecologic surgery, but in line with the conclusions of the meta-analysis, it may be that the timing of TAP block administration was the difference between benefit (preoperative)⁵⁸ and no benefit (postoperative).⁵⁹

One prospective, case-matched study in laparoscopic colorectal surgery incorporated TAP blocks into an established ERAS protocol, enabling further reduction of postoperative pain, opioid consumption, and hospital length of stay (median of 3 d vs 2 d).⁶⁰ The benefits of TAP blocks should be further studied in RCTs to assess their value as a part of ERAS protocols in gynecologic surgery.

Local anesthetic wound infusion

A large systematic review of 45 RCTs⁶¹ reported that surgical wound catheter infiltration with local anesthetic provides effective postoperative analgesia, reducing overall pain scores and minimizing opioid consumption compared with an opioid-based analgesic technique. Although there were positive results for the subcategory of gynecology-urology procedures, cesarean sections and prostatectomies comprised 50% of these studies. A summary of studies in gynecologic surgery alone is presented in **Table 5**. For major gynecologic surgery, the benefits of subcutaneous local anesthetic wound infiltration were seen only with larger-volume (9 mL) intermittent boluses⁶² but not lower-volume (2 mL) continuous local anesthetic infusions.^{63,64} The location of the catheter is important to provide effective analgesia, because even higher-volume local anesthetic infiltration below the muscle layers did not provide effective analgesia as subcutaneous and intraperitoneal infiltration catheters.^{62,65,66} Subcutaneous infiltration provided better patient satisfaction and lower pain scores and opioid consumption when compared directly with intraperitoneal infiltration.^{65,67}

Local anesthetic wound infiltration

RCTs using incisional and deep wound infiltration with local anesthetic before skin closure did not reduce opioid consumption in patients undergoing hysterectomy.^{68,69} RCTs studying preincisional local anesthetic infiltration reported a minimal reduction in opioid consumption in hysterectomies⁷⁰ and no opioid-sparing effect in laparotomies for gynecologic cancer.⁷¹ Neither preincisional nor postincisional local anesthetic wound infiltration was effective in reducing pain scores or opioid consumption for laparoscopic gynecologic surgery.⁷² Only 1 study in highly motivated patients undergoing pelvic organ prolapse surgery⁷³ reported that this surgery could be performed under local anesthetic infiltration alone, and compared with general anesthesia, this technique was more cost effective, but no benefit was seen in opioid use, PONV, or hospital length of stay. Taken together, these trials show little to no effect of local anesthetic wound infiltration for gynecologic surgeries.

Intraperitoneal local anesthetics

The analgesic effect of intraperitoneal administration of a single dose of local anesthetics intraoperatively in patients undergoing open abdominal hysterectomy has yielded conflicting results.^{74,75} However, a meta-analysis has confirmed the analgesic efficacy of continuous infusion of intraperitoneal local anesthetics.⁷⁶ Up to 40% opioid-sparing effects were reported with this technique after open abdominal hysterectomy,⁷⁷ with better efficacy using a patient-controlled technique compared with a continuous infusion.⁷⁸ Opioid-sparing effects of intraperitoneal lidocaine were greater compared with IV lidocaine after abdominal hysterectomy.⁷⁹

OTHER OPIOID-SPARING MULTIMODAL ANALGESIC STRATEGIES FOR MAJOR GYNECOLOGIC SURGERY

γ-Aminobutyric Acid Analogs

In a recent meta-analysis of 6 RCTs,⁸⁰ preoperatively administered pregabalin reduced 24-hour morphine consumption (weighted mean difference -8.5 mg [95% confidence interval (CI), -5.71 to -11.29]) and postoperative pain scores compared with controls after major gynecologic surgery. There was a significant reduction in PONV with pregabalin at the expense of increased dizziness.⁸⁰ The dose range was 100 to 300 mg once or repeated every 8 to 12 hours.⁸⁰ A recent meta-analysis⁸¹ suggested that for acute pain outcomes, there does not seem to be a significant benefit from repeated doses of pregabalin compared with a single dose administered before surgery and that analgesia was comparable with doses ranging from 100 to 300 mg.

In a meta-analysis of 14 RCTs using preoperative gabapentin for abdominal hysterectomy,⁸² overall 24-hour morphine consumption was reduced from 24.3 to 55.9 mg to 13.2 to 42.7 mg, with a standardized mean difference of -0.67 (95% CI -1.2 to -0.07). When gabapentin was used preoperatively and postoperatively, the 24-hour morphine consumption was reduced from 25.7 to 80 mg to 20.3 to 55 mg, with a standardized mean difference of -1.45 (95% CI -1.79 to -1.11).⁸² Most studies administered gabapentin 1 to 2 hours preoperatively in a single dose of 1200 mg or with smaller doses of 100 to 400 mg administered every 6 to 8 hours.⁸² Dose-ranging studies in other patient populations suggest that the minimum effective dose of preoperative gabapentin is 600 mg.⁸³ PONV was also reduced in the gabapentin group, with no increased incidence of somnolence or dizziness compared with the control group.⁸² Similar to pregabalin, combined preoperative and postoperative doses of gabapentin did not confer advantages compared with preoperative-only administration.⁸² The potential side effects of these 2 drugs reported in meta-analyses of their perioperative use include sedation and visual disturbances.⁸¹

Arachidonic Acid Metabolism Inhibitors

Arachidonic acid is converted into prostaglandins via 2 cyclooxygenase (COX-1 and COX-2) pathways.⁸⁴ The uterus expresses both COX-1 and COX-2 at different levels throughout the menstrual cycle, making these ideal medications for use in gynecologic surgeries.⁸⁴

In a meta-analysis of nonsteroidal antiinflammatory drugs (NSAIDs) and COX-2 inhibitors in all types of surgery, morphine-sparing effects of those agents were comparable with an approximate average reduction of 10 mg of morphine in 24 hours compared with placebo,⁸⁵ but the reduction in opioid-related side effects such as nausea was seen only with NSAIDs. The opioid-sparing effect of these agents ranged from 22% to 50% in different studies in patients undergoing gynecologic surgery.^{86–96} Although increased risk of bleeding is a theoretical concern with perioperative use of NSAIDs, a recent meta-analysis⁹⁷ suggested that perioperative ketorolac does not increase risk of bleeding.

Paracetamol (Acetaminophen) and Propacetamol

The IV formulation of paracetamol has been available in Europe since 2001 and was approved in the United States in 2010. Systematic reviews^{85,98} show that both paracetamol and propacetamol reduce opioid consumption by 30%, which is equally efficacious to NSAIDs in the postoperative period for all-type surgery. Most studies in the gynecologic surgery population report an opioid-sparing effect of 30% to 40% with a 1-g to 2-g once-daily or twice-daily dosing regimen.^{99–101} These agents have been

Table 5
Summary of the effects of wound infiltration catheters using local anesthetics on ERAS principles in major gynecologic surgery

Type of Surgery	Study	Group Allocation (Number of patients)	Wound Infiltration Catheter	Other ERAS Interventions	ERAS Outcomes
Laparotomy for gynecologic cancer ^a	Kushner et al, ⁶⁴ 2005	LA catheter group (N = 40) Control catheter group (N = 40)	Location: subcutaneous Infusion: continuous bupivacaine 0.5% or saline at 2 mL/h	None specified	No difference: Pain scores Opioid consumption Time to first defecation Hospital length of stay
Abdominal hysterectomy ^b	Leong et al, ⁶³ 2002	LA catheter group (N = 26) Control group: no catheter (N = 26)	Location: subcutaneous Infusion: continuous bupivacaine 0.5% at 2 mL/h	None specified	No difference: Pain scores Opioid consumption
Abdominal hysterectomy ^c	Zohar et al, ⁶² 2001	LA catheter group (N = 18) Control catheter group (N = 18)	Location: subcutaneous Infusion: PCA Bupivacaine 0.25% or saline \leq 9 mL/h	Multimodal analgesia regimen	Favors subcutaneous instillation with LA: Reduced pain scores (VAS ~20 lower) Reduced morphine consumption in recovery room (mean 6 vs 12 mg) Reduced meperidine consumption overall (mean 29 vs 95 mg) Lower incidence of nausea (antiemetic treatment 44% vs 100%) Higher patient satisfaction (78% vs 39% rated analgesia good or excellent) Shorter hospital length of stay (6 vs 7 d)

Abdominal hysterectomy ^b	Kristensen et al, ⁶⁶ 1999	LA catheter group (N = 22) Control catheter group (N = 19)	Location: bilateral catheters on each side of the incision, below muscle layer, above peritoneum Infusion: bupivacaine 0.25% or saline 15 mL each catheter every 4 h	None specified	No difference: Pain scores Opioid consumption
Abdominal hysterectomy ^b	Gupta et al, ⁶⁵ 2004	LA catheter group (N = 20) Control catheter group (N = 20)	Location: intraperitoneal supracervical area Infusion: levobupivacaine 0.25% or saline at 5 mL/h	None specified	Favors intraperitoneal instillation with LA Lower pain scores first 2 h (VAS ~20 lower) Reduced ketobemidone consumption at 4–24 h (mean 19 vs 31 mg) Reduced incidence of nausea (15% vs 50%) No difference: Hospital length of stay Time to mobilization

Abbreviations: LA, local anesthetic; PCA, patient-controlled analgesia.

^a Malignant and benign indication.

^b Benign indication.

^c Indication not specified.

Data from Refs.^{62–66}

compared directly with NSAIDs in the gynecologic surgery patient population, with equal efficacy to ketorolac¹⁰² but slightly less efficacy compared with diclofenac.^{87,103} A recent systematic review¹⁰⁴ also reported a reduction in PONV with the use of IV paracetamol. Additional opioid-sparing effects and PONV reduction are obtained when combining NSAIDs with paracetamol than either drug alone.^{103,105}

Lidocaine Infusion

Meta-analyses and systematic reviews^{106,107} reported that IV lidocaine infusions reduced postoperative pain, decreased opioid consumption, led to faster return of bowel function, and shortened hospital length of stay in abdominal surgeries. However, studies of patients undergoing open or laparoscopic hysterectomy have not shown benefits in reducing pain scores, opioid consumption, improving quality of recovery, or shortening hospital stays,^{108–110} except for some reduction in inflammatory mediators and pain scores in the early postoperative period in 1 study.¹¹⁰ The lack of analgesic benefit may be because the lidocaine infusions were used only in the intraoperative period in these trials. Although many studies of other abdominal surgeries continued the lidocaine infusion in the postoperative period, some studies also reported benefit after administration only in the intraoperative period.¹⁰⁶

Ketamine Infusion

A meta-analysis of 70 studies¹¹¹ concluded that ketamine infusions improve postoperative analgesia and reduce opioid consumption, particularly in upper abdominal, thoracic, and major orthopedic procedures. Studies of ketamine use in women undergoing gynecologic surgery have yielded conflicting results. In an RCT in patients undergoing hysterectomy, an intraoperative ketamine infusion reduced morphine consumption by 35%, improved pain scores at 8 to 12 hours after surgery, and improved patient satisfaction with analgesia but did not promote faster return of bowel function or faster ambulation or reduce hospital length of stay.¹¹² Another RCT in a gynecologic surgery patient population¹¹³ found that a preincision bolus followed by an intraoperative infusion or a bolus of ketamine at wound closure was more effective at reducing pain scores and morphine consumption (by 50%) than 1 preincision dose of ketamine. In patients undergoing myomectomies or hysterectomies for fibroids, no difference in pain scores or opioid consumption was found after a preincision bolus and intraoperative and postoperative infusion of ketamine.¹⁰⁸ The ketamine infusion dosing regimens varied greatly between studies, with initial dosing of 0.3 mg/kg to 0.5 mg/kg and a continuous infusion of 50 µg to 600 µg/kg/h intraoperatively only or up to 24 hours postoperatively.^{108,112,113} It is unclear whether ketamine would provide routine benefit to gynecologic surgery patients or its use should be limited to certain patients, such as those with chronic pain conditions who are on long-term opioids.

REDUCING POSTOPERATIVE NAUSEA AND VOMITING AFTER MAJOR GYNECOLOGIC SURGERY

The Apfel simplified risk score for prediction of PONV includes 4 factors: female gender, history of PONV or motion sickness, nonsmoking status, and need for postoperative opioids.¹¹⁴ Most women in the United States (82%) are nonsmokers, and major gynecologic surgery requires postoperative opioids, so this patient population typically has starting PONV risk of 60% according to the Apfel score.¹¹⁵ Furthermore, although it has been debated whether the type of surgery is a risk factor for PONV, a meta-analysis of risk factors¹¹⁶ reported that gynecologic surgery is an independent risk factor for PONV.

The Society for Ambulatory Anesthesia consensus guidelines for PONV recommend combination antiemetic therapy in this high-risk patient population and adoption of strategies to reduce the baseline risk of PONV.¹¹⁷

STRATEGIES TO REDUCE THE BASELINE RISK OF POSTOPERATIVE NAUSEA AND VOMITING

Avoid General Anesthesia by Using Regional Anesthesia

The use of regional anesthesia has been associated with up to 9-fold reduction in the incidence of PONV.¹¹⁸ However, the influence of neuraxial analgesia on PONV is variable, depending on the technique used and the type of epidural medications administered. Compared with general anesthesia with an opioid-based analgesic technique, spinal anesthesia reduces PONV only if no or low-dose (60 µg) intrathecal morphine is used.^{33,119}

Most studies using epidural analgesia for major gynecologic surgery combine this technique with general anesthesia, and this might not reduce PONV. Callesen and colleagues¹¹⁹ compared PONV rates between an opioid-free combined spinal-epidural (CSE) technique (local anesthetic alone) and a general anesthetic group with epidural analgesia (local anesthetic and opioid) in patients undergoing hysterectomy. The cumulative 72-hour incidence of PONV was 50% in the CSE group and 100% in the combined general anesthetic with epidural group.¹¹⁹ However, the need for supplementary opioids was higher in the CSE group.

Avoid Inhaled Agents and Nitrous Oxide if General Anesthesia Is Used

Inhaled agents increase the risk of PONV, particularly in the early postoperative period.¹²⁰ Nitrous oxide is associated with increased risk of PONV, particularly in women.¹²¹ Total IV anesthesia with propofol is associated with a reduction in the risk of PONV, particularly in the first 6 hours after surgery, with a number needed to treat of 5.¹²²

Minimize Intraoperative and Postoperative Opioids

Opioid-sparing techniques are an integral part of ERAS protocols, because they not only reduce PONV but also affect other opioid-related side effects that can affect patients' recovery and delay discharge, such as sedation and postoperative ileus. Despite the opioid-sparing effects of these interventions, their effects on reducing PONV are not consistent. A reduction in the risk of PONV was reported with intraperitoneal local anesthetic instillation catheters^{77,79} but not with TAP blocks or subcutaneous infiltration catheters.^{56,62,65} The γ -aminobutyric acid analogs show consistent reduction in PONV.^{80,82} A meta-analysis including all types of surgery¹²³ reported a reduction in PONV with NSAIDs but not with COX-2 inhibitors. In a systematic review of 30 RCTs, IV paracetamol provided better analgesia and reduced PONV, despite no reduction in opioid consumption.^{98,104}

Adequate Hydration

Intraoperative fluid management and its effects on ERAS principles, including PONV, seem to be highly dependent on the surgery, more specifically the length and extent of surgical damage. A systematic review of 80 studies¹²⁴ concluded that in minor and moderate ambulatory surgeries, including laparoscopic gynecologic surgeries, PONV could be reduced in patients receiving more liberal regimens (1–2 L of fluid). In 1 RCT in women with 2 to 4 risk factors for PONV having laparoscopic gynecologic surgery,¹²⁵ the liberal fluid group (3 mL/kg/h of fasting) had lower rates of PONV (59% vs 87%) than the restrictive group (2 mL/kg/h of fasting). Lower PONV rates were also

Table 6
Summary of goal-directed fluid therapy on ERAS outcomes for major gynecologic surgery

Reference, Surgery Type	Study Type	Description of Fluid Management (Number of Patients)		Other ERAS Interventions	Summary of ERAS Outcomes
McKenny et al, ¹³¹ 2013 Laparotomy gynecologic cancer surgery	RCT	Control (N = 50) Fluid management at the anesthesiologist's discretion for: Urine output <0.5 mL/kg/h Unspecified increase in heart rate Unspecified decrease in SBP Unspecified decrease in CVP Replacement of estimated intraoperative losses	Intervention (N = 51) SV measurement via esophageal Doppler US Algorithm: HES administered 3 mL/kg X1 SV >10% response, give another 3 mL/kg, until SV responds <10%, SV <10% response, repeat SV measurement 15 min.	No ERAS protocol in the gynecologic surgery population at this institution	No reduction in hospital length of stay No difference in postoperative morbidity score No difference in gastrointestinal recovery
Chattopadhyay et al, ¹³² 2013 Laparotomy gynecologic cancer surgery	Prospective observational study	Control Advanced stage (N = 62) Early stage (N = 57) Hemodynamic-based fluid management Not specified	Intervention Advanced stage (N = 44) Early stage (N = 35) SV measurement via esophageal Doppler US No algorithm specified	No ERAS protocol specified	Favors goal-directed therapy in advanced-stage disease only: Goal-directed fluid therapy associated with earlier postoperative recovery ^a (OR 2.8) Less PONV in goal-directed therapy (9% vs 24%)

Gan et al, ¹³³ 2002 Mixed major abdominal surgery ^b	RCT	Control (N = 50) Bolus 5 mL/kg LR followed by 5 mL/kg/h infusion during surgery	Intervention (N = 50) Bolus 5 mL/kg LR followed by 5 mL/ kg/h infusion during surgery Algorithm: 200 mL HES if FTc ^c <0.35 s If SV > or = by the fluid challenge and FTc <0.35 s: fluid challenge was repeated If SV >10% and FTc >0.35 s, fluid challenge repeated until no further increase in SV occurred If FTc >0.40 s and = SV, further fluid was not given until SV decreased by 10% of the last value	No ERAS protocol specified	Favors goal-directed therapy: Shorter length of hospital stay in goal-directed therapy (median 5 vs 7 d) Faster oral intake (3 vs 4.7 d) Less PONV requiring antiemetic therapy (14% vs 36%)
---	-----	---	--	----------------------------------	---

Abbreviations: CVP, central venous pressure; FTc, corrected flow time; HES, hydroxyethyl starch; LR, lactated Ringer; OR, odds ratio; SBP, systolic blood pressure; SV, stroke volume; US, ultrasonography.

^a Early postoperative recovery defined as ≥ 2 of the following: mobilization on the first postoperative day, oral diet resumption on postoperative day 1; and return of bowel function on postoperative day 4 or earlier.

^b Major elective general, urologic, or gynecologic surgery with anticipated blood loss >500 mL.

^c FTc: aortic systolic flow time corrected for heart rate: index of systemic vascular resistance that is sensitive to changes in left ventricular preload.

Data from Refs.^{131–133}

reported¹²⁶ in patients undergoing either laparoscopic gynecologic procedure or a cholecystectomy in a liberal fluid management group 15 mL/kg bolus (23%) versus the conservative fluid management group 2 mg/kg bolus (73%). A meta-analysis including 15 studies, 11 of which included patients undergoing gynecologic surgery, reported that compared with conservative fluid regimens, administration of supplemental IV crystalloids reduced the risk of early postoperative nausea (relative risk 0.73, 95% CI 0.59–0.89), postoperative nausea at 24-hour (relative risk 0.41, 95% CI 0.22–0.76), and overall 24-hour postoperative nausea (relative risk 0.66, 95% CI 0.46–0.95). Liberal IV crystalloids also reduced overall 24-hour PONV (relative risk 0.48, 95% CI 0.29–0.79), late PONV (relative risk 0.27, 95% CI 0.13–0.54), and overall 24-hour PONV (relative risk 0.59, 95% CI 0.42–0.84), as well as the need for antiemetic rescue treatment (relative risk 0.56, 95% CI 0.45–0.68).¹²⁷

ANTIEMETIC PROPHYLAXIS

Because the gynecologic patient population is at high risk for PONV, combination antiemetic therapy should be used for prophylaxis. Studies have consistently reported the superior antiemetic efficacy of combination therapy compared with single-agent antiemetic prophylaxis. The multimodal approach incorporates combination antiemetic therapy in addition to measures to reduce the baseline risk of PONV, as discussed earlier, and should be used in high-risk patients.¹¹⁷ The most commonly investigated therapies include a combination of 5-HT₃ antagonists with either dexamethasone or droperidol, with both combinations having comparable antiemetic efficacy.^{128,129} Longer-acting antiemetics might provide additional protection against delayed PONV and postdischarge nausea and vomiting. Those agents include palonosetron, transdermal scopolamine, and the neurokinin-1 receptor antagonist aprepitant, with the last one being significantly more effective than ondansetron in prophylaxis against vomiting in women undergoing major gynecologic surgery.¹³⁰

FLUID MANAGEMENT FOR MAJOR GYNECOLOGIC SURGERY

In contrast to ambulatory surgeries, in which PONV may be the primary outcome of concern, for major nonvascular abdominal surgeries, goal-directed fluid management improves major outcomes, such as cardiopulmonary function, gastric motility, and wound healing, and reduces hospital length of stay.¹²⁴ However, studies investigating goal-directed therapy in gynecologic surgery are limited. **Table 6**^{131–133} summarizes the studies in gynecologic surgery examining the impact of intraoperative fluid administration regimen on patients' outcomes. A meta-analysis of 32 trials by Cecconi and colleagues¹³⁴ reported that patients with the highest risk of surgical mortality benefited the most from goal-directed therapy, which seems to be supported by 1 prospective observational trial in patients undergoing laparotomies for gynecologic cancer.¹³² RCTs are clearly lacking in the gynecologic surgery population with regards to whether goal-directed fluid therapy confers benefits in these patients.

OTHER ENHANCED RECOVERY AFTER SURGERY PRINCIPLES FOR MAJOR GYNECOLOGIC SURGERY

Other elements of ERAS for major gynecologic surgeries include the approach to preoperative preparation, bowel management, surgical approach, thromboprophylaxis, and postoperative planning. A summary of the literature regarding those elements in the gynecologic patient population is presented in **Table 7**.

Table 7
Summary of outcomes in major gynecologic surgery when comparing a traditional approach with ERAS interventions

Traditional Approach	ERAS Intervention	Study Outcomes
Lack of focus on preoperative nutrition	Improve nutritional status	No known effective strategies identified in patients with ovarian cancer ¹³⁶
Bowel preparations	No bowel preparations	Bowel preparations ^{137–139} Do not: Prevent infection Improve surgical visualization Do: Reduce patient satisfaction
Routine NG tubes	No routine NG tubes	NG tubes ¹⁴⁰ Do not: Reduce postoperative ileus Reduce aspiration Do: Increase aspiration risk Increase patient discomfort
Delayed feeding	Early feeding	Early feeding ^{141,142} Does: Promote early return of bowel function Shorten HLOS Increase nausea
±Antibiotic prophylaxis	Appropriate antibiotic prophylaxis	Antibiotic prophylaxis ^{143,144} Indicated: all open procedures Unclear indication: some laparoscopic procedures Not indicated: minor or intrauterine procedures
Open procedures	Minimally invasive procedures when feasible	Hysterectomies ¹ VH vs AH: VH has less blood loss, fastest recovery, shortest HLOS, lowest infection rate VH vs LH: VH has less blood loss, lower infection rate Laparoscopic vs open for all gynecologic surgeries ^{1,145} Advantage: Less pain Less blood loss Shorter HLOS Disadvantage: Increased urinary tract injuries Robotic ¹⁴⁶ : No RCTs comparing robotic procedures with laparoscopic or open procedures

(continued on next page)

Traditional Approach	ERAS Intervention	Study Outcomes
No routine thromboprophylaxis	Routine thromboprophylaxis	<p>Patients with ovarian cancer¹⁴⁷: Heparin SQ 3 times daily to prevent thromboembolism No increase in bleeding complications</p> <p>Laparoscopic procedures¹⁴⁸: Unclear if needed in minor laparoscopic procedures More extensive surgeries increase the risk of thromboembolism, so prophylaxis warranted</p> <p>Hysterectomy¹⁴⁹: Pharmaceutical prophylaxis highly effective Possible increased risk of postoperative bleeding</p>
Drains, tubes, catheters placed	No drains, tubes, catheters	Early removal of urinary catheters reduces HLOS ¹⁴²
Discharge patient when they are ready	Preplanning discharge	Scant literature on this topic in gynecology literature ¹⁴²

Abbreviations: AH, abdominal hysterectomy; HLOS, hospital length of stay; LH, laparoscopic hysterectomy; NG, nasogastric; SQ, subcutaneous; VH, vaginal hysterectomy.

SUMMARY

- Studies on ERAS after gynecologic surgery are limited and mainly extrapolate several ERAS principles from colorectal surgery and apply them to gynecologic surgery to a variable extent. Similar outcome benefits, namely a reduction in hospital length of stay, have been reported in those studies.
- Despite recommendations for use of regional anesthesia for colorectal procedures, an ideal, standardized anesthetic technique has not been identified, and thus, it is important to evaluate the best evidence for regional techniques in gynecologic surgery when developing ERAS guidelines in this surgical population.
- Effective regional anesthetic techniques in gynecologic surgery include spinal anesthesia, epidural analgesia, TAP blocks, local anesthetic instillation catheters, and intraperitoneal local anesthetic instillation.
- Effective nonopioid analgesics include pregabalin, gabapentin, NSAIDs, COX-2 inhibitors, and paracetamol.
- Ketamine infusions may provide benefit for some patients after major gynecologic surgery but should not be used routinely. Lidocaine infusions, although effective in other abdominal surgeries, provide no benefit for gynecologic surgery.
- A multimodal antiemetic strategy must be used, including strategies to reduce the baseline risk of PONV in conjunction with combination antiemetic therapy.
- RCTs exploring fluid management strategies on ERAS outcomes in the major gynecologic surgery population are lacking.
- Anesthesiologists should be aware of all ERAS principles from colorectal surgery that are also beneficial in major gynecologic surgery, such as bowel management, goal-directed fluid management strategies, timely administration of appropriate antibiotics, and thromboprophylaxis, because many of these may become quality measures for anesthesiologists in the future.

REFERENCES

1. Nieboer TE, Johnson N, Lethaby A, et al. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev* 2009;(3):CD003677.
2. Fleming ND, Havrilesky LJ, Valea FA, et al. Analgesic and antiemetic needs following minimally invasive vs open staging for endometrial cancer. *Am J Obstet Gynecol* 2011;204:65.e1–6.
3. Zhuang CL, Ye XZ, Zhang XD, et al. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: a meta-analysis of randomized controlled trials. *Dis Colon Rectum* 2013;56:667–78.
4. Spanjersberg WR, Reurings J, Keus F, et al. Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database Syst Rev* 2011;(2):CD007635.
5. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002;183:630–41.
6. Campesi I, Fois M, Franconi F. Sex and gender aspects in anesthetics and pain medication. *Handb Exp Pharmacol* 2012;(214):265–78.
7. Ottesen M, Sorensen M, Rasmussen Y, et al. Fast track vaginal surgery. *Acta Obstet Gynecol Scand* 2002;81:138–46.
8. Kroon UB, Radstrom M, Hjelthe C, et al. Fast-track hysterectomy: a randomised, controlled study. *Eur J Obstet Gynecol Reprod Biol* 2010;151:203–7.
9. Kalogera E, Bakkum-Gamez JN, Jankowski CJ, et al. Enhanced recovery in gynecologic surgery. *Obstet Gynecol* 2013;122:319–28.
10. Dickson E, Argenta PA, Reichert JA. Results of introducing a rapid recovery program for total abdominal hysterectomy. *Gynecol Obstet Invest* 2012;73:21–5.
11. Marx C, Rasmussen T, Jakobsen DH, et al. The effect of accelerated rehabilitation on recovery after surgery for ovarian malignancy. *Acta Obstet Gynecol Scand* 2006;85:488–92.
12. Sjetne IS, Krogstad U, Odegard S, et al. Improving quality by introducing enhanced recovery after surgery in a gynaecological department: consequences for ward nursing practice. *Qual Saf Health Care* 2009;18:236–40.
13. Yoong W, Sivashanmugarajan V, Relph S, et al. Can enhanced recovery pathways improve outcomes of vaginal hysterectomy? Cohort control study. *J Minim Invasive Gynecol* 2014;21:83–9.
14. Wijk L, Franzen K, Ljungqvist O, et al. Implementing a structured enhanced recovery after surgery (ERAS) protocol reduces length of stay after abdominal hysterectomy. *Acta Obstet Gynecol Scand* 2014;93:749–56.
15. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br J Anaesth* 2010;105:106–15.
16. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 2014;112:991–1004.
17. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. *Gastroenterol Res Pract* 2014;2014:141737.
18. Carli F, Kehlet H, Baldini G, et al. Evidence basis for regional anesthesia in multidisciplinary fast-track surgical care pathways. *Reg Anesth Pain Med* 2011;36:63–72.
19. Beattie WS, Badner NH, Choi PT. Meta-analysis demonstrates statistically significant reduction in postoperative myocardial infarction with the use of thoracic epidural analgesia. *Anesth Analg* 2003;97:919–20.

20. Hahnenkamp K, Herroeder S, Hollmann MW. Regional anaesthesia, local anaesthetics and the surgical stress response. *Best Pract Res Clin Anaesthesiol* 2004; 18:509–27.
21. Hart SR, Bordes B, Hart J, et al. Unintended perioperative hypothermia. *Ochsner J* 2011;11:259–70.
22. Jorgensen H, Wetterslev J, Moiniche S, et al. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev* 2000;(4):CD001893.
23. Kabon B, Fleischmann E, Treschan T, et al. Thoracic epidural anesthesia increases tissue oxygenation during major abdominal surgery. *Anesth Analg* 2003;97:1812–7.
24. Popping DM, Elia N, Marret E, et al. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg* 2008;143:990–9 [discussion: 1000].
25. Guay J. The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. *J Anesth* 2006;20:335–40.
26. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003;290:2455–63.
27. Andraea MH, Andraea DA. Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery. *Cochrane Database Syst Rev* 2012;(10):CD007105.
28. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* 2000;321:1493.
29. Sprung J, Sanders MS, Warner ME, et al. Pain relief and functional status after vaginal hysterectomy: intrathecal versus general anesthesia. *Can J Anaesth* 2006;53:690–700.
30. Catro-Alves LJ, De Azevedo VL, De Freitas Braga TF, et al. The effect of neuraxial versus general anesthesia techniques on postoperative quality of recovery and analgesia after abdominal hysterectomy: a prospective, randomized, controlled trial. *Anesth Analg* 2011;113:1480–6.
31. Borendal Wodlin N, Nilsson L, Carlsson P, et al. Cost-effectiveness of general anesthesia vs spinal anesthesia in fast-track abdominal benign hysterectomy. *Am J Obstet Gynecol* 2011;205(326):e1–7.
32. Massicotte L, Chalaoui KD, Beaulieu D, et al. Comparison of spinal anesthesia with general anesthesia on morphine requirement after abdominal hysterectomy. *Acta Anaesthesiol Scand* 2009;53:641–7.
33. Vaida SJ, Ben David B, Somri M, et al. The influence of preemptive spinal anesthesia on postoperative pain. *J Clin Anesth* 2000;12:374–7.
34. Ferguson SE, Malhotra T, Seshan VE, et al. A prospective randomized trial comparing patient-controlled epidural analgesia to patient-controlled intravenous analgesia on postoperative pain control and recovery after major open gynecologic cancer surgery. *Gynecol Oncol* 2009;114:111–6.
35. Katz J, Cohen L, Schmid R, et al. Postoperative morphine use and hyperalgesia are reduced by preoperative but not intraoperative epidural analgesia: implications for preemptive analgesia and the prevention of central sensitization. *Anesthesiology* 2003;98:1449–60.
36. Jorgensen H, Fomsgaard JS, Dirks J, et al. Effect of peri- and postoperative epidural anaesthesia on pain and gastrointestinal function after abdominal hysterectomy. *Br J Anaesth* 2001;87:577–83.

37. Chinachoti T, Niruthisard S, Tuntisirin O, et al. A double-blind, randomized study comparing postoperative pain management using epidural ropivacaine with intravenous ketorolac or intravenous ketorolac alone following transabdominal hysterectomy. *J Med Assoc Thai* 2002;85(Suppl 3):S837–47.
38. Wattwil M, Thoren T, Hennerdal S, et al. Epidural analgesia with bupivacaine reduces postoperative paralytic ileus after hysterectomy. *Anesth Analg* 1989; 68:353–8.
39. Thorn SE, Wattwil M, Kallander A. Effects of epidural morphine and epidural bupivacaine on gastroduodenal motility during the fasted state and after food intake. *Acta Anaesthesiol Scand* 1994;38:57–62.
40. Geddes SM, Thorburn J, Logan RW. Gastric emptying following caesarean section and the effect of epidural fentanyl. *Anaesthesia* 1991;46:1016–8.
41. Vallejo MC, Edwards RP, Shannon KT, et al. Improved bowel function after gynecological surgery with epidural bupivacaine-fentanyl than bupivacaine-morphine infusion. *Can J Anaesth* 2000;47:406–11.
42. Asantila R, Eklund P, Rosenberg PH. Continuous epidural infusion of bupivacaine and morphine for postoperative analgesia after hysterectomy. *Acta Anaesthesiol Scand* 1991;35:513–7.
43. Thoren T, Sundberg A, Wattwil M, et al. Effects of epidural bupivacaine and epidural morphine on bowel function and pain after hysterectomy. *Acta Anaesthesiol Scand* 1989;33:181–5.
44. Blythe JG, Hodel KA, Wahl TM, et al. Continuous postoperative epidural analgesia for gynecologic oncology patients. *Gynecol Oncol* 1990;37:307–10.
45. Rapp SE, Ready LB, Greer BE. Postoperative pain management in gynecology oncology patients utilizing epidural opiate analgesia and patient-controlled analgesia. *Gynecol Oncol* 1989;35:341–4.
46. de Leon-Casasola OA, Parker BM, Lema MJ, et al. Epidural analgesia versus intravenous patient-controlled analgesia. Differences in the postoperative course of cancer patients. *Reg Anesth* 1994;19:307–15.
47. Rivard C, Dickson EL, Vogel RI, et al. The effect of anesthesia choice on postoperative outcomes in women undergoing exploratory laparotomy for a suspected gynecologic malignancy. *Gynecol Oncol* 2014;133:278–82.
48. Chen LM, Weinberg VK, Chen C, et al. Perioperative outcomes comparing patient controlled epidural versus intravenous analgesia in gynecologic oncology surgery. *Gynecol Oncol* 2009;115:357–61.
49. Belavy D, Janda M, Baker J, et al. Epidural analgesia is associated with an increased incidence of postoperative complications in patients requiring an abdominal hysterectomy for early stage endometrial cancer. *Gynecol Oncol* 2013;131:423–9.
50. Lin L, Liu C, Tan H, et al. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. *Br J Anaesth* 2011;106:814–22.
51. Capmas P, Billard V, Gouy S, et al. Impact of epidural analgesia on survival in patients undergoing complete cytoreductive surgery for ovarian cancer. *Anticancer Res* 2012;32:1537–42.
52. de Oliveira GS Jr, Ahmad S, Schink JC, et al. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. *Reg Anesth Pain Med* 2011;36:271–7.
53. Lacassie HJ, Cartagena J, Branes J, et al. The relationship between neuraxial anesthesia and advanced ovarian cancer-related outcomes in the Chilean population. *Anesth Analg* 2013;117:653–60.

54. Tonnesen E, Wahlgreen C. Influence of extradural and general anaesthesia on natural killer cell activity and lymphocyte subpopulations in patients undergoing hysterectomy. *Br J Anaesth* 1988;60:500–7.
55. Hong JY, Lim KT. Effect of preemptive epidural analgesia on cytokine response and postoperative pain in laparoscopic radical hysterectomy for cervical cancer. *Reg Anesth Pain Med* 2008;33:44–51.
56. Champaneria R, Shah L, Geoghegan J, et al. Analgesic effectiveness of transversus abdominis plane blocks after hysterectomy: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2013;166:1–9.
57. De Oliveira GS Jr, Castro-Alves LJ, Nader A, et al. Transversus abdominis plane block to ameliorate postoperative pain outcomes after laparoscopic surgery: a meta-analysis of randomized controlled trials. *Anesth Analg* 2014;118:454–63.
58. De Oliveira GS Jr, Fitzgerald PC, Marcus RJ, et al. A dose-ranging study of the effect of transversus abdominis block on postoperative quality of recovery and analgesia after outpatient laparoscopy. *Anesth Analg* 2011;113:1218–25.
59. Kane SM, Garcia-Tomas V, Alejandro-Rodriguez M, et al. Randomized trial of transversus abdominis plane block at total laparoscopic hysterectomy: effect of regional analgesia on quality of recovery. *Am J Obstet Gynecol* 2012;207:419.e1–5.
60. Favuzza J, Brady K, Delaney CP. Transversus abdominis plane blocks and enhanced recovery pathways: making the 23-h hospital stay a realistic goal after laparoscopic colorectal surgery. *Surg Endosc* 2013;27:2481–6.
61. Liu SS, Richman JM, Thirlby RC, et al. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg* 2006;203:914–32.
62. Zohar E, Fredman B, Phillipov A, et al. The analgesic efficacy of patient-controlled bupivacaine wound instillation after total abdominal hysterectomy with bilateral salpingo-oophorectomy. *Anesth Analg* 2001;93:482–7, 4th contents page.
63. Leong WM, Lo WK, Chiu JW. Analgesic efficacy of continuous delivery of bupivacaine by an elastomeric balloon infusor after abdominal hysterectomy: a prospective randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2002;42:515–8.
64. Kushner DM, LaGalbo R, Connor JP, et al. Use of a bupivacaine continuous wound infusion system in gynecologic oncology: a randomized trial. *Obstet Gynecol* 2005;106:227–33.
65. Gupta A, Perniola A, Axelsson K, et al. Postoperative pain after abdominal hysterectomy: a double-blind comparison between placebo and local anesthetic infused intraperitoneally. *Anesth Analg* 2004;99:1173–9 Table of contents.
66. Kristensen BB, Christensen DS, Ostergaard M, et al. Lack of postoperative pain relief after hysterectomy using preperitoneally administered bupivacaine. *Reg Anesth Pain Med* 1999;24:576–80.
67. Hafizoglu MC, Katircioglu K, Ozkalkanli MY, et al. Bupivacaine infusion above or below the fascia for postoperative pain treatment after abdominal hysterectomy. *Anesth Analg* 2008;107:2068–72.
68. Cobby TF, Reid MF. Wound infiltration with local anaesthetic after abdominal hysterectomy. *Br J Anaesth* 1997;78:431–2.
69. Klein JR, Heaton JP, Thompson JP, et al. Infiltration of the abdominal wall with local anaesthetic after total abdominal hysterectomy has no opioid-sparing effect. *Br J Anaesth* 2000;84:248–9.

70. Hannibal K, Galatius H, Hansen A, et al. Preoperative wound infiltration with bupivacaine reduces early and late opioid requirement after hysterectomy. *Anesth Analg* 1996;83:376–81.
71. Updike GM, Manolitsas TP, Cohn DE, et al. Pre-emptive analgesia in gynecologic surgical procedures: preoperative wound infiltration with ropivacaine in patients who undergo laparotomy through a midline vertical incision. *Am J Obstet Gynecol* 2003;188:901–5.
72. Fong SY, Pavy TJ, Yeo ST, et al. Assessment of wound infiltration with bupivacaine in women undergoing day-case gynecological laparoscopy. *Reg Anesth Pain Med* 2001;26:131–6.
73. Segal JL, Owens G, Silva WA, et al. A randomized trial of local anesthesia with intravenous sedation vs general anesthesia for the vaginal correction of pelvic organ prolapse. *Int Urogynecol J Pelvic Floor Dysfunct* 2007;18:807–12.
74. Ng A, Swami A, Smith G, et al. The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine after total abdominal hysterectomy. *Anesth Analg* 2002;95:158–62 Table of contents.
75. Ali PB, Cotton BR, Williamson KM, et al. Intraperitoneal bupivacaine or lidocaine does not provide analgesia after total abdominal hysterectomy. *Br J Anaesth* 1998;80:245–7.
76. Kahokehr A, Sammour T, Soop M, et al. Intraperitoneal local anaesthetic in abdominal surgery—a systematic review. *ANZ J Surg* 2011;81:237–45.
77. Gupta N, Dadhwal V, Mittal S. Combined intraperitoneal instillation and port site infiltration of local anaesthetic (bupivacaine) for postoperative analgesia in women undergoing daycare diagnostic gynaecological laparoscopy. *Eur J Obstet Gynecol Reprod Biol* 2012;161:109–10.
78. Perniola A, Fant F, Magnuson A, et al. Postoperative pain after abdominal hysterectomy: a randomized, double-blind, controlled trial comparing continuous infusion vs patient-controlled intraperitoneal injection of local anaesthetic. *Br J Anaesth* 2014;112:328–36.
79. Perniola A, Magnuson A, Axelsson K, et al. Intraperitoneal local anesthetics have predominant local analgesic effect: a randomized, double-blind study. *Anesthesiology* 2014;121:352–61.
80. Yao Z, Shen C, Zhong Y. Perioperative pregabalin for acute pain after gynecological surgery: a meta-analysis. *Clin Ther* 2014. [Epub ahead of print].
81. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. *Br J Anaesth* 2015;114:10–31.
82. Alayed N, Alghanaim N, Tan X, et al. Preemptive use of gabapentin in abdominal hysterectomy: a systematic review and meta-analysis. *Obstet Gynecol* 2014;123:1221–9.
83. Pandey CK, Navkar DV, Giri PJ, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar discectomy: a randomized, double-blind, placebo-controlled study. *J Neurosurg Anesthesiol* 2005;17:65–8.
84. Hayes EC, Rock JA. COX-2 inhibitors and their role in gynecology. *Obstet Gynecol Surv* 2002;57:768–80.
85. Maund E, McDaid C, Rice S, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. *Br J Anaesth* 2011;106:292–7.
86. Ng A, Parker J, Toogood L, et al. Does the opioid-sparing effect of rectal diclofenac following total abdominal hysterectomy benefit the patient? *Br J Anaesth* 2002;88:714–6.

87. Cobby TF, Crighton IM, Kyriakides K, et al. Rectal paracetamol has a significant morphine-sparing effect after hysterectomy. *Br J Anaesth* 1999;83:253–6.
88. Scott RM, Jennings PN. Rectal diclofenac analgesia after abdominal hysterectomy. *Aust N Z J Obstet Gynaecol* 1997;37:112–4.
89. Blackburn A, Stevens JD, Wheatley RG, et al. Balanced analgesia with intravenous ketorolac and patient-controlled morphine following lower abdominal surgery. *J Clin Anesth* 1995;7:103–8.
90. Balestrieri P, Simmons G, Hill D, et al. The effect of intravenous ketorolac given intraoperatively versus postoperatively on outcome from gynecologic abdominal surgery. *J Clin Anesth* 1997;9:358–64.
91. Rogers JE, Fleming BG, Macintosh KC, et al. Effect of timing of ketorolac administration on patient-controlled opioid use. *Br J Anaesth* 1995;75:15–8.
92. Ng A, Smith G, Davidson AC. Analgesic effects of parecoxib following total abdominal hysterectomy. *Br J Anaesth* 2003;90:746–9.
93. Nong L, Sun Y, Tian Y, et al. Effects of parecoxib on morphine analgesia after gynecology tumor operation: a randomized trial of parecoxib used in postsurgical pain management. *J Surg Res* 2013;183:821–6.
94. Barton SF, Langeland FF, Snabes MC, et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. *Anesthesiology* 2002;97:306–14.
95. Viscusi ER, Frenkl TL, Hartrick CT, et al. Perioperative use of etoricoxib reduces pain and opioid side-effects after total abdominal hysterectomy: a double-blind, randomized, placebo-controlled phase III study. *Curr Med Res Opin* 2012;28:1323–35.
96. Chau-in W, Thienthong S, Pulnitiporn A, et al. Prevention of post operative pain after abdominal hysterectomy by single dose etoricoxib. *J Med Assoc Thai* 2008;91:68–73.
97. Gobble RM, Hoang HL, Kachniarz B, et al. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg* 2014;133:741–55.
98. McNicol ED, Tzortzopoulou A, Cepeda MS, et al. Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. *Br J Anaesth* 2011;106:764–75.
99. Arici S, Gurbet A, Turker G, et al. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri* 2009;21:54–61.
100. Olonisakin RP, Amanor-Boadu SD, Akinyemi AO. Morphine-sparing effect of intravenous paracetamol for post operative pain management following gynaecological surgery. *Afr J Med Med Sci* 2012;41:429–36.
101. Moon YE, Lee YK, Lee J, et al. The effects of preoperative intravenous acetaminophen in patients undergoing abdominal hysterectomy. *Arch Gynecol Obstet* 2011;284:1455–60.
102. Varrassi G, Marinangeli F, Agro F, et al. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. *Anesth Analg* 1999;88:611–6.
103. Montgomery JE, Sutherland CJ, Kestin IG, et al. Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination. *Br J Anaesth* 1996;77:445–7.
104. Apfel CC, Turan A, Souza K, et al. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. *Pain* 2013;154:677–89.

105. Ong CK, Seymour RA, Lirk P, et al. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg* 2010;110:1170–9.
106. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs* 2010;70:1149–63.
107. Vigneault L, Turgeon AF, Cote D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. *Can J Anaesth* 2011;58:22–37.
108. Grady MV, Mascha E, Sessler DI, et al. The effect of perioperative intravenous lidocaine and ketamine on recovery after abdominal hysterectomy. *Anesth Analg* 2012;115:1078–84.
109. Bryson GL, Charapov I, Krolczyk G, et al. Intravenous lidocaine does not reduce length of hospital stay following abdominal hysterectomy. *Can J Anaesth* 2010; 57:759–66.
110. Yardeni IZ, Beilin B, Mayburd E, et al. The effect of perioperative intravenous lidocaine on postoperative pain and immune function. *Anesth Analg* 2009; 109:1464–9.
111. Laskowski K, Stirling A, McKay WP, et al. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth* 2011;58:911–23.
112. Sen H, Sizlan A, Yanarates O, et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. *Anesth Analg* 2009;109:1645–50.
113. Bilgin H, Ozcan B, Bilgin T, et al. The influence of timing of systemic ketamine administration on postoperative morphine consumption. *J Clin Anesth* 2005; 17:592–7.
114. Apfel CC, Laara E, Koivuranta M, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology* 1999;91:693–700.
115. Centers for Disease Control and Prevention. Current cigarette smoking among adults—United States, 2005–2012. *MMWR Morb Mortal Wkly Rep* 2014;63(2): 29–34.
116. Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth* 2012;109: 742–53.
117. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014;118:85–113.
118. Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? *Anesthesiology* 1999;91:109–18.
119. Callesen T, Schouenborg L, Nielsen D, et al. Combined epidural-spinal opioid-free anaesthesia and analgesia for hysterectomy. *Br J Anaesth* 1999;82:881–5.
120. Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br J Anaesth* 2002;88:659–68.
121. Fernandez-Guisasola J, Gomez-Arnau JI, Cabrera Y, et al. Association between nitrous oxide and the incidence of postoperative nausea and vomiting in adults: a systematic review and meta-analysis. *Anaesthesia* 2010;65:379–87.
122. Tramer M, Moore A, McQuay H. Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *Br J Anaesth* 1997;78:247–55.
123. McDaid C, Maund E, Rice S, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction

- of morphine-related side effects after major surgery: a systematic review. *Health Technol Assess* 2010;14:1–153, iii–iv.
124. Holte K, Kehlet H. Fluid therapy and surgical outcomes in elective surgery: a need for reassessment in fast-track surgery. *J Am Coll Surg* 2006;202:971–89.
 125. Maharaj CH, Kallam SR, Malik A, et al. Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. *Anesth Analg* 2005;100:675–82 Table of contents.
 126. Ali SZ, Taguchi A, Holtmann B, et al. Effect of supplemental pre-operative fluid on postoperative nausea and vomiting. *Anaesthesia* 2003;58:780–4.
 127. Apfel CC, Meyer A, Orhan-Sungur M, et al. Supplemental intravenous crystalloids for the prevention of postoperative nausea and vomiting: quantitative review. *Br J Anaesth* 2012;108:893–902.
 128. Habib AS, El-Moalem HE, Gan TJ. The efficacy of the 5-HT₃ receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone. A meta-analysis of randomized controlled trials. *Can J Anaesth* 2004;51:311–9.
 129. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004;350:2441–51.
 130. Gan TJ, Apfel CC, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesth Analg* 2007;104:1082–9 Tables of contents.
 131. McKenny M, Conroy P, Wong A, et al. A randomised prospective trial of intraoperative oesophageal Doppler-guided fluid administration in major gynaecological surgery. *Anaesthesia* 2013;68:1224–31.
 132. Chattopadhyay S, Mittal S, Christian S, et al. The role of intraoperative fluid optimization using the esophageal Doppler in advanced gynecological cancer: early postoperative recovery and fitness for discharge. *Int J Gynecol Cancer* 2013;23:199–207.
 133. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002;97:820–6.
 134. Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: goal-directed therapy—what is the evidence in surgical patients? The effect on different risk groups. *Crit Care* 2013;17:209.
 135. de Groot JJ, van Es LE, Maessen JM, et al. Diffusion of enhanced recovery principles in gynecologic oncology surgery: is active implementation still necessary? *Gynecol Oncol* 2014;134:570–5.
 136. Billson HA, Holland C, Curwell J, et al. Perioperative nutrition interventions for women with ovarian cancer. *Cochrane Database Syst Rev* 2013;(9):CD009884.
 137. Siedhoff MT, Clark LH, Hobbs KA, et al. Mechanical bowel preparation before laparoscopic hysterectomy: a randomized controlled trial. *Obstet Gynecol* 2014;123:562–7.
 138. Lijoi D, Ferrero S, Mistrangelo E, et al. Bowel preparation before laparoscopic gynaecological surgery in benign conditions using a 1-week low fibre diet: a surgeon blind, randomized and controlled trial. *Arch Gynecol Obstet* 2009;280:713–8.
 139. Ballard AC, Parker-Autry CY, Markland AD, et al. Bowel preparation before vaginal prolapse surgery: a randomized controlled trial. *Obstet Gynecol* 2014;123:232–8.

140. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev* 2007;(3):CD004929.
141. Charoenkwan K, Phillipson G, Vutyavanich T. Early versus delayed (traditional) oral fluids and food for reducing complications after major abdominal gynaecologic surgery. *Cochrane Database Syst Rev* 2007;(4):CD004508.
142. Murphy M, Olivera C, Wheeler T 2nd, et al. Postoperative management and restrictions for female pelvic surgery: a systematic review. *Int Urogynecol J* 2013;24:185–93.
143. Morrill MY, Schimpf MO, Abed H, et al. Antibiotic prophylaxis for selected gynecologic surgeries. *Int J Gynaecol Obstet* 2013;120:10–5.
144. Van Eyk N, van Schalkwyk J. Antibiotic prophylaxis in gynaecologic procedures. *J Obstet Gynaecol Can* 2012;34:382–91.
145. Lin YS. Preliminary results of laparoscopic modified radical hysterectomy in early invasive cervical cancer. *J Am Assoc Gynecol Laparosc* 2003;10:80–4.
146. Weinberg L, Rao S, Escobar PF. Robotic surgery in gynecology: an updated systematic review. *Obstet Gynecol Int* 2011;2011:852061.
147. Einstein MH, Kushner DM, Connor JP, et al. A protocol of dual prophylaxis for venous thromboembolism prevention in gynecologic cancer patients. *Obstet Gynecol* 2008;112:1091–7.
148. Bouchard-Fortier G, Geerts WH, Covens A, et al. Is venous thromboprophylaxis necessary in patients undergoing minimally invasive surgery for a gynecologic malignancy? *Gynecol Oncol* 2014;134:228–32.
149. Brummer TH, Heikkinen A, Jalkanen J, et al. Pharmaceutical thrombosis prophylaxis, bleeding complications and thromboembolism in a national cohort of hysterectomy for benign disease. *Hum Reprod* 2012;27:1628–36.