

# Preoperative Orthostatic Dysfunction Is Associated with an Increased Incidence of Postoperative Nausea and Vomiting

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**Background:** Postoperative nausea and vomiting (PONV) occurs frequently after gynecologic surgery. Because hemodynamic condition seems to be influential, women presenting with preoperative orthostatic dysregulation may have an increased risk for PONV. The aim of the present study was to assess the relationship between preoperative orthostatic dysregulation and the incidence of PONV.

**Methods:** In a prospective observer-blinded clinical trial, 200 women who were scheduled for elective gynecologic surgery underwent an orthostatic test on the day before surgery. Based on the orthostatic test results, women were stratified into orthostatic dysregulation (OR; systolic blood pressure decrease > 20 mmHg on standing up) and nonorthostatic dysregulation (NOR; systolic blood pressure decrease < 20 mmHg) groups.

**Results:** Forty-nine women were stratified to the OR group and 151 to the NOR group. Frequencies of PONV and vomiting during the study period were higher in the OR group compared with the NOR group (77.6% vs. 31.1% and 55.1 vs. 18.5%, respectively; all  $P < 0.001$ ). Women with hypotension in their history showed a significantly higher frequency of PONV within 24 h ( $P < 0.05$ ).

**Conclusion:** Women presenting with orthostatic dysregulation and arterial hypotension in their history exhibit an increased risk of PONV.

TECHNICAL equipment and anesthetic drugs available are continuously improving, but postoperative nausea and vomiting (PONV) remains a frequent and unpleasant incident in daily anesthesia practice. Different risk scores were introduced to help discriminate patients who are at risk for PONV and those who are not.<sup>1,2</sup> Female gender, history of motion sickness or previous PONV, nonsmoking, and the use of postoperative opioid drugs were demonstrated to be independent predictors of PONV.<sup>1-3</sup> Risk scores may help us to develop and evaluate target-directed therapies in the future.

The influence of hemodynamic variables on PONV has been repeatedly considered. Blood pressure (BP) abnormalities, autonomic nervous system disturbance, and orthostatic hypotension are of major importance for the

occurrence of vertigo, dizziness, and probably of PONV.<sup>4</sup> Preexisting autonomic nervous system dysfunction may be further aggravated by periods of systemic hypotension, especially during anesthesia induction and postoperative transport of the patient to the recovery room. Perioperative stress leads to a change in adrenergic activity.<sup>5</sup> Women's endocrinologic status influences vasoconstrictor sensitivity.<sup>6</sup> Further, BP-stabilizing drugs have been found to be effective in PONV prophylaxis.<sup>7</sup>

We hypothesized that the incidence of PONV is higher in women presenting with preoperative orthostatic dysregulation and in women with systemic arterial hypotension in their history. The aim of the present study was to evaluate the incidence of orthostatic dysregulation in preoperative unselected gynecologic patients and its association with PONV.

## Materials and Methods

This study was performed after review by the institutional ethics commission and with patients' written informed consent. We studied 200 women with American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective gynecologic surgery. Only non-pregnant women independent of menstrual cycle phase were recruited. Women presenting with significant cardiac disease (New York Heart Association [NYHA] class > 1) or dysfunction of their vestibular system were excluded.

On the day before surgery, women were interviewed during routine preoperative medical and physical assessment for details of previous anesthesia, PONV, and history of motion sickness. Age, weight, and the date of their last menstruation were recorded for all women. Patients were asked for history of hypotension (< 100/60 mmHg), hypertension (> 140/90 mmHg), dizziness, or fainting on standing up. Preoperative anxiety was identified by the use of a visual analog scale (VAS), choosing VAS score more than 4 as a cut-off value for preoperative anxiety.<sup>8</sup>

An orthostatic test was performed on the day before surgery to evaluate systemic BP and heart rate (HR) response to body position changes.<sup>4</sup> BP was measured using a mercury sphygmomanometer with cuffs appropriate to the arm circumference. HR was registered simultaneously in the supine position. Repeated values for BP and HR were assessed after 1 and 10 min in supine position. Thereafter, patients were asked to stand up

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quickly and remain standing for 10 min. BP and HR were registered in the standing position at 1, 5, and 10 min. The last values for HR and BP in the supine position were our reference values for comparison with the lowest BP and the highest HR values in the standing position. Values were not averaged. All measurements were performed using a commonly available transport monitor (M3046A, Agilent Technologies, Boeblingen, Germany). Women were classified as positive for orthostatic dysregulation if systolic BP dropped more than 20 mmHg in either measurement.<sup>9</sup> Based on the orthostatic test results, women were stratified to the positive orthostatic test group (OR group) or the negative orthostatic test group (NOR group).

The fasting status was uniform in all women, allowing them to eat a light meal and to drink until 6 h before surgery. All women were premedicated with midazolam, 7.5 mg, given orally 1 h before the transport to the operating room. In the operating room, standard monitoring consisting of electrocardiography, noninvasive BP (NIBP) monitoring, pulseplethysmography, oxygen-saturation, and end tidal CO<sub>2</sub> was applied. The anesthetist providing general anesthesia to the study patient was blinded to the results of the orthostatic test. Immediately before anesthesia induction, an infusion of lactated Ringer's solution was started, and the patients received 10 ml · kg<sup>-1</sup> · h<sup>-1</sup> intraoperatively. Anesthesia was induced with intravenous fentanyl (2–3 µg/kg) and propofol (2 mg/kg). Muscle relaxation was achieved using rocuronium (0.6 mg/kg) and was monitored continuously using a peripheral nerve stimulator. Anesthesia was maintained with nitrous oxide (70%), oxygen (30%), and sevoflurane. Repeated doses of fentanyl, 0.05–0.1 mg, were administered at discretion of anesthetists. Normoventilation was maintained (end tidal CO<sub>2</sub>, 32–36 mmHg). A nasogastric tube was inserted immediately after intubation to drain gases or gastric contents from the stomach. Before tracheal extubation, the nasogastric tube was suctioned and removed. At the end of the surgical procedure, intravenous atropine, 0.02 mg/kg, and neostigmine, 0.04 mg/kg, were administered for reversal of muscle relaxation. Women received either nonsteroidal analgesic drugs or bolus doses of piritramide, 3 mg, for postoperative analgesia as required. Within the first 2 h postoperatively, all patients received 5 ml · kg<sup>-1</sup> · h<sup>-1</sup> of lactated Ringer's solution. Women were allowed to drink after the first 2 h. During the immediate postoperative observation period (0–2 h), an anesthetist blinded to the results of the orthostatic test assessed nausea and vomiting. On the ward, trained nurses blinded to the results of the orthostatic tests observed the women during the late observation period (3–24 h) for nausea and vomiting. Women presenting with nausea (VAS > 4)<sup>10</sup> or vomiting (*i.e.*, who felt PONV) received 5 mg of intravenous tropisetron as rescue medication. Those with consistent complaints (>

1 h) after the rescue medication received another 2 mg of tropisetron. The Apfel risk score consisting of four predictors for PONV—female gender, history of motion sickness or previous PONV, nonsmoking, and the use of postoperative opioid agents—was calculated for the women. All predictors were uniform weighted as 1, if present, or 0, if absent.<sup>3</sup>

### Statistical Analysis

All data are presented as mean ± SD and frequencies. Normality of distribution was assessed by Kolmogorov-Smirnov test. Differences of continuous variables between groups were compared using Student *t* test. For comparison of proportional data, chi-square tests were performed. A *P* value less than 0.05 was considered significant. A logistic regression model was performed for the Apfel risk score, for positive orthostatic dysregulation, and for both factors together as independent predictors of PONV (all predictors were uniform weighted as 1, if the factor was present, or 0, if absent). For estimation of the discrimination power of the Apfel risk score in our data, of the preoperative positive orthostatic test, and of both together, receiver operating characteristic curves (ROC) were plotted. The 95% confidence intervals (95%CI) of the area under the curve (AUC) were calculated.

A power analysis was calculated before the study as follows. We assumed a 20% difference in the incidence of PONV between the groups. From historical data in similar patients, we estimated the prevalence of PONV to be 40%. We attempted to have a power of at least 90% at a significance level of *P* = 0.05 to detect a potential difference between the groups. This analysis revealed a minimum number of 134 patients. To further strengthen the power, we included 200 women in the study.

## Results

Two hundred women were recruited to the investigation. According to the results of the preoperative orthostatic tests, 49 women (24.5%) were assigned to the OR group, and the remaining 151 (75.5%) women were assigned to the NOR group. While standing upright for 10 min, systolic BP decreased 32 mmHg (SD, 10 mmHg) in the OR group compared with 8 mmHg (SD, 7 mmHg) in the NOR group (*P* < 0.001). HR increased 23 beats/min (SD, 10 beats/min) in the OR group compared with 13 beats/min (SD, 8 beats/min) in the NOR group (*P* < 0.001). No differences in the type and frequency of surgical procedures occurred between the groups (table 1). Descriptive data for age, weight, height, body mass index, preoperative anxiety, phase of menstrual cycle, number of women taking antihypertensives or hormone replacement therapy, intraoperative fentanyl dosage required, number of women who received postoperative

**Table 1. Type of Surgery, Patients' Characteristics and Variables of Apfel's Risk Score According to Orthostatic Tests**

	OR-group (n = 49)	NOR-group (n = 151)
Hysteroscopy n (%)	11 (22.4)	43 (28.5)
Vulvovaginal surgery n (%)	4 (8.2)	14 (9.3)
Incontinence surgery n (%)	1 (2.0)	8 (5.3)
Laparotomy n (%)	21 (42.9)	44 (29.1)
Hysterectomy n (%)	10 (20.4)	38 (25.2)
Others n (%)	2 (4.1)	4 (2.6)
Age yr (range)	53 (29–81)	52 (22–80)
Height cm (range)	164 (154–176)	164 (150–180)
Weight kg (range)	66 (49–97)	71 (42–130)*
Body mass index kg · m <sup>-2</sup> (range)	24.5 (18.2–35.6)	26.6 (17.9–41.5)*
Preoperative anxiety VAS (range)	4.0 (0–10)	4.3 (0–10)
Menstruation cycle	12/14/23	19/50/82
Day 1–8/day 9–30/menopause n (%)	24.4/28.6/46.9	12.6/33.1/54.3
Women taking antihypertensives n (%)	12 (24.5)	24 (15.9)
Women taking hormone replacement n (%)	1 (2.0)	11 (7.3)
Duration of anesthesia min (range)	118 (20–307)	106 (20–400)
Duration of operation min (range)	84 (10–255)	70 (10–345)
Intraoperative fentanyl mg (range)	0.34 (0.1–0.6)	0.31 (0.1–0.8)
Postop piritramide mg (range)	9.2 (0–36)	9.9 (0–36)
Nonsmoking n (%)	35 (71.4)	98 (64.9)
Previous PONV n (%)	21 (42.9)*	38 (25.2)
Motion sickness n (%)	18 (36.7)	39 (25.8)
Postoperative opioid n (%)	35 (71.4)	102 (67.5)
Apfel score 1/2/3/4 n (%)	4/7/24/14	11/46/63/31
Mean expected risk for PONV (95% CI) of the OR and NOR group in consideration of Apfel score <sup>3</sup>	(8.2/14.3/49.0/28.6) 59% (55–64%)	(7.3/30.5/42.0/20.5) 55% (52–58%)

Comparison between OR-group (positive orthostatic test group) and NOR-group (negative orthostatic test group); frequencies are given as n = number and (%), continuous data are presented as mean (range); \* =  $P < 0.05$ .

PONV = postoperative nausea and vomiting.

opioid agents and the amount of, duration of anesthesia, and duration of surgery are shown in table 1. No hemodynamic differences between the OR and NOR groups were found intraoperatively with regard to the maximum decrease of systolic BP (24% [SD, 11%] vs. 22% [11%], respectively;  $P = 0.41$ ) nor for the lowest intraoperative HR (58 beats/min [SD, 13 beats/min] vs. 59 beats/min [9 beats/min], respectively;  $P = 0.32$ ). Hypoxia ( $\text{SaO}_2 < 94\%$ ; duration  $> 1$  min) did not occur in any patient.

Parameters of the risk score according to Apfel<sup>3</sup> and the percentage of women presenting with self-reported hypotension, hypertension, or orthostatic complaints in their history are shown in table 1. No differences between the OR group and NOR group were found for the Apfel risk score ( $P = 0.158$ ). More women with history of previous PONV were found in the OR group ( $P < 0.05$ ).

The overall frequencies of nausea and vomiting were higher in the OR group compared with the NOR group (table 2). Reflecting the whole population within the immediate observation period, nausea and vomiting occurred in 41% (n = 82) and 26% (n = 52), respectively. Within the late observation period, nausea and vomiting have been found in 19.5% (n = 39) and 8% (n = 16), respectively. Chi-square test of the whole study population showed increased Apfel risk scores in patients suffering from nausea (chi-square = 24.6;  $P < 0.001$ ) and

vomiting (chi-square = 15.7;  $P = 0.001$ ) within the immediate observation period. In the late observation period, differences were significant for nausea but not for vomiting (chi-square = 10.9;  $P = 0.012$  and chi-square = 6.4;  $P = 0.09$ , respectively). All women of the OR and NOR groups who felt nauseous (VAS  $> 4$ ) or vomited received a first dose of tropisetron, 5 mg (38 [77.6%] and 47 [34%], respectively). From those women, 18 (47%) of the OR group and 16 (34%) of the NOR group received a second dose of intravenous tropisetron, 2 mg;  $P = 0.21$ .

Logistic regression analysis revealed the following for our data. Apfel score: sensitivity, 36.5%; specificity, 87.8%; positive predictive value, 68.9%; negative predictive value, 65.2%; area under the ROC curve, 0.70 (95%CI, 0.63–0.77). Orthostatic dysregulation: sensitivity, 44.7%; specificity, 90.4%; positive predictive value, 77.6%; negative predictive value, 68.9%; AUC, 0.68 (95%CI, 0.60–0.75). Apfel score + orthostatic dysregulation: sensitivity, 62.4%; specificity, 80%; positive predictive value, 69.7%; negative predictive value, 74.2%; AUC, 0.77 (95%CI, 0.70–0.83).

There was no difference in the incidence of orthostatic reaction in women with or without hypotension in their history ( $P = 0.15$ ). However, women with a history of dizziness or fainting on standing upright had a higher incidence of orthostatic reaction (chi-square = 27.3;  $P <$



**Table 2. Incidence of PONV Depending on Discussed Risk Factors**

Risk Factor	Women with the Risk Factor N (%)	PONV		Vomiting	
		Yes	No	Yes	No
Orthostatic dysfunction	49 (24.5)	77.6††	55.1††	31.1	18.5
Hypotension	57 (28.5)	56.1*	36.8	37.1	23.8
Hypertension	70 (35.0)	40.0	25.7	43.8	28.5
Dizziness on standing	53 (26.5)	62.3††	35.8	35.4	24.5
Fainting on standing	18 (9.0)	61.1	44.4	40.7	25.8
Menstrual	31 (15.5)	54.8	35.5	40.2	26.0
Postmenstrual	64 (32.0)	43.8	28.1	41.9	27.2
Postmenopausal	105 (52.5)	38.1	24.8	47.4	30.5
Preoperative anxiety	92 (46.0)	43.5	31.5	41.7	24.1
Motion sickness	57 (28.5)	50.9	36.8	39.2	23.8
Previous PONV	59 (29.5)	62.7††	45.8††	34.0	19.9
Non-smoking	133 (66.5)	48.1*	31.6	31.3	19.4
Postoperative opioids	137 (68.5)	50.4††	32.8*	25.4	15.9
Apfel risk score >2	132 (66.0)	53.8††	36.4††	20.6	10.3

Incidences of risk factors presented in n (%). Incidences of PONV (PONV = postoperative nausea and vomiting > VAS 4) and vomiting within the first 24 hours given in % of women with (= yes) and without (= no) the risk factor. No women vomited without nausea, therefore nausea was not presented separately.

\* =  $P < 0.05$ ; †† =  $P < 0.001$ .

0.001 and chi-square = 10.3;  $P = 0.001$ , respectively). An association between a positive orthostatic test and the menstrual cycle could not be demonstrated ( $P = 0.135$ ; table 1). Incidences of PONV in women with a self-reported history of arterial hypotension, dizziness on standing up, and fainting on standing are given in table 2.

## Discussion

The main result of this prospective clinical investigation was that the risk of PONV within the first 24 h after gynecologic surgery is significantly increased in women presenting with preoperative orthostatic dysregulation. We demonstrated a relatively high incidence of orthostatic dysfunction and PONV in the studied patients collective (24.5%). The following factors may be responsible for these findings: First, insufficient preoperative fluid intake during the last days before surgery probably aggravates preexisting cardiovascular instability and orthostatic dysfunction. Second, it has been suggested that stress occurring during the preoperative period leads to a change in adrenergic activity.<sup>11</sup> Persistent exposure to catecholamines results in lowered responsiveness of target cells to further stimulus by agonists through a phenomenon known as desensitization.<sup>5</sup> Hyperadrenergic orthostatic intolerance may occur during times of emotional excitement,<sup>12</sup> although we could not establish any correlation between the incidence of PONV and preoperative anxiety, as assessed by VAS. Third, occurrence of orthostatic intolerance may be related to sex hormones. Orthostatic intolerance is remarkably overrepresented in premenopausal women.<sup>12</sup> Variations in the endocrinologic status dependent upon menstrual cycle seem to influence vasoconstrictor sensitivity.<sup>6</sup> Women during the follicular phase of the menstrual cycle (characterized by high endogenous estrogen serum levels, unopposed

by progesterone) are relatively insensitive to the vasoconstrictor action of norepinephrine. Further, it has been shown that estrogen replacement therapy reduces vasoconstrictor response to norepinephrine in perimenopausal women, possibly by increased nitric oxide synthesis. However, we could not demonstrate an association between the menstrual cycle and the incidence of PONV (table 2). Additionally, no relation was found between the menstrual cycle and orthostatic dysregulation (table 1).

A series of animal and human studies have demonstrated that the neurotransmitter serotonin (5-hydroxytryptamine) plays an essential role in the central regulation of BP and HR.<sup>9</sup> Serotonin reuptake inhibitors can be effective in the management of neurocardiogenic syncope and orthostatic hypotension.<sup>9</sup> Granisetron, a 5-HT<sub>3</sub>-receptor antagonist, administered intravenously immediately before induced hemorrhage altered the Bezold-Jarisch reflex (*i.e.*, hypotension and inappropriate HR slowing) in an animal model.<sup>13</sup>

The present study reveals an association between preoperative orthostatic dysfunction and the incidence of PONV after gynecologic surgery. However, the prediction of PONV for a particular patient remains difficult. We were able to demonstrate that orthostatic dysregulation is a significant independent predictor of PONV, but failed to add a clinically relevant factor that substantially improves a prediction model, improving the area under the ROC curve only from 0.70 to 0.77 in women.

In conclusion, our data show a strong association between orthostatic dysregulation and PONV. More specific studies are required to investigate the underlying mechanisms of the possible influence of orthostatic dysregulation on the pathogenesis of PONV, especially in men. Confirmation of the present results may lead to new approaches to the prevention and therapy of PONV.

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