

SUMMARY OF CONSENSUS OPINION

Scientific Panel on GYNECARE VERSAPOINT

**Meeting Date: October 15, 2000
Los Angeles, CA**

A. BACKGROUND

On September 22, 2000, GYNECARE, a division of ETHICON, INC., undertook a voluntary global withdrawal of the *GYNECARE VERSAPOINT Bipolar Electrosurgery System* electrodes and handpieces in response to a small number of spontaneous reports of non-fatal air and gas embolism associated with use of the system during hysteroscopic myomectomy procedures. This withdrawal was performed in the interest of patient safety, in order to allow a full and thorough assessment of the technical issues, surgical technique and circumstances associated with these events.

As part of the post-withdrawal investigation, GYNECARE convened a panel of scientific and clinical experts with the express purpose of reappraising the reported cases of air and gas embolism, reviewing the current knowledge of gas and air emboli in hysteroscopic surgery, and establishing an appropriate and necessary research strategy directed at assessing the relative safety of the GYNECARE VERSAPOINT system. Drawn from a group of experts in hysteroscopic surgery and cardiopulmonary medicine, the panel consisted of the following members:

Andrew Brill, MD

Professor, University of Illinois at Chicago,
Department of Obstetrics and Gynecology, Director,
Gynecologic Endoscopy, Chicago, IL
Associate Clinical Professor of Obstetrics and
Gynecology, University of Arizona, Phoenix, AZ;
Medical Director, American Association of
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Frank Loffer, MD

Eduardo H. Rubinstein, MD, PhD	Professor of Physiology and Anesthesiology, University of California, Los Angeles, CA
Barbara Levy, MD	Assistant Clinical Professor of Obstetrics & Gynecology, University of Washington School of Medicine, Federal Way, WA; Chairman, Continuing Medical Education Committee, American Association of Gynecologic Laparoscopists
Gilbert Johnston, MD	Adult Cardiac Surgery, Adult and Pediatric Thoracic Surgery, Tacoma, WA
Malcolm Munro, MD	Professor, Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, CA
Michel Vleugels, MD, PhD	Co-Director Registrar Training Gynecology, Canisius Wilhelmina Hospital, Nijmegen, Netherlands
Martin Farrugia, MD, MRCOG	Clinical Research Fellow in Gynaecological Endoscopy, Whipps Cross Hospital, London, England
Stefano Bettocchi, MD	Assistant Gynecologist, OB/GYN Dept., Policlinico II, Bari, Italy
Herve Fernandez, MD	Professor of Obstetrics and Gynecology, Paris 11 University, Paris, France

After careful review and deliberation, the panel has produced this consensus statement summarizing its findings, recommendations and conclusions as pertains to the case reports, the practice of hysteroscopy in consideration of the risks of gas and air embolism, and the scientific studies necessary to justify reintroduction of the GYNECARE VERSAPOINT system into the therapeutic marketplace.

B. APPRAISAL OF CASE REPORTS

GYNECARE has received seven spontaneous reports of gas or air embolism since acquiring the technology from Gynecare, Inc. (Menlo Park, CA) in 1997. All cases were investigated upon receipt of the complaint and Medical Device Reports (MDRs) were duly filed with the FDA. Further information about each of the cases was obtained through review of supplemental records and additional directed questioning of the involved surgeon and/or anesthesiologist subsequent to the withdrawal of the device.

One additional, prior case was reported to and evaluated by Gynecare, Inc. (Menlo Park, CA) in 1997.

The Panel reviewed all relevant case details, and reached a consensus on each case regarding the likely diagnosis and clinical significance of the adverse event.

Consensus Statement: Appraisal of Cases

The panel observed that gas and room air venous emboli have different etiologies and different clinical significance. Gas emboli in hysteroscopic electrosurgery likely arise from the intra-venous entrainment of the gaseous by-products of electrosurgery. Room air embolism in hysteroscopy, by contrast, arises from the active or passive intra-venous entrainment of air introduced into the uterus via a piston-like action of the instruments during insertion, non-purged air in the fluid in-flow line, a patulous cervix open to air subsequent to disruption of uterine sinusoids, and cervical lacerations associated with dilatation.

Room air embolism is an inherent risk in all uterine surgery. Literature from the last 25 years documents many cases of air embolism, most fatal, associated with hysterectomy, cesarean section, cervical dilatation, dilatation and curettage, laparoscopy, diagnostic hysteroscopy and operative hysteroscopy.

Since room air embolization is an intrinsic risk of uterine surgery and does not arise from activation of the electrosurgical device, the panel concluded that the four cases judged to be probable air emboli should not be considered device related and thus should not be included in an analysis of device-related risk.

The panel concluded that only the suspected gas emboli are potentially attributable to the device and thus relevant to the risk analysis of the GYNECARE VERSAPOINT system.

Moreover, the panel concluded that the case reported to Gynecare Inc. in 1997 was not likely a hysteroscopy-related embolism, and thus should also be removed from consideration in assessing the embolic risk of the GYNECARE VERSAPOINT system.

Thus, three cases in the consensus opinion of the panel, remain under consideration as possible gas emboli, although in each room air emboli cannot be ruled out definitively. These three cases include two with the Zero Degree Vaporizing electrode, and one with the 5Fr Twizzle Tip electrode.

Additionally, the panel observed that in each of these cases, the diagnosis of air and gas embolism was a presumptive, clinical diagnosis: none of the patients had doppler (precordial or esophageal) that might have more definitively demonstrated the presence of emboli.

Consensus Statement: True Incidence of Events

The panel observed that calculated incidence rates arising from spontaneously reported cases (i.e., complaints) are not true incidence rates. The true incidence of room air and gas embolism in uterine surgery overall is likely grossly under reported. Subtle, transient physiologic abnormalities, as in several of these cases, may be overlooked in the course of surgery, particularly in cases under regional or local anesthesia where end-tidal CO₂ is not routinely monitored. Many cases of room air/gas emboli may be being misdiagnosed as fluid overload which can have a similar clinical presentation.

The true incidence of room air and gas embolism associated with hysteroscopic electrosurgery is altogether unknown.

The panel concluded, therefore, that it is inappropriate and invalid to conclude that the incidence or risk of gas embolism is higher with the GYNECARE VERSAPOINT system than with any other hysteroscopic electrosurgical device. The panel suggested that it is likely that monopolar and bipolar hysteroscopic devices would have similar risks of gas embolism.

Consensus Statement: Relative Safety of Monopolar Devices

The panel observed that in excess of 500,000 hysteroscopic electrosurgical procedures have been performed in the U.S. alone in the last 15 years. The vast majority has involved monopolar electrosurgical devices. Despite this extensive experience, the panel observed that there is no acknowledgement among gynecologists that monopolar electrosurgery is risky in terms of gas embolism.

The Panel acknowledged that there is concern in the hysteroscopic community about other significant risks associated with monopolar electrosurgery in non-electrolyte solutions (i.e., fluid overload, hyponatremia, cerebral edema).

The panel concluded, based upon the accepted safety of monopolar electrosurgery, that it is reasonable, valid and acceptable to establish the safety (vis-a-vis gas embolism) of the GYNECARE VERSAPOINT system by comparing the device to monopolar electrosurgical devices used for similar indications.

Consensus Statement of the Panel: Seriousness and Significance of Events

None of the reported cases of gas or room air embolism resulted in patient death or permanent injury. Appropriate monitoring and early detection by anesthesiologists allowed for timely diagnosis and successful intervention.

Room air and gas emboli in hysteroscopy remain potentially serious and life-threatening events nonetheless. The panel agreed that these disorders are largely under-recognized and under-appreciated in the surgical community.

The panel concluded that knowledgeable physicians and medical societies have a duty to further educate and warn practicing hysteroscopists and anesthesiologists about the risks of gas and room air embolism associated with hysteroscopic surgery and thereby decrease the risk of serious sequelae.

The panel resolved to publish a set of recommendations to hysteroscopists and anesthesiologists intended to increase the awareness of these complications during operative hysteroscopy.

C. RECOMMENDATIONS OF THE PANEL FOR REDUCING EMBOLIC RISK IN OPERATIVE HYSTEROSCOPY

Based on its collective experience and expertise, and a current review of the world literature, the panel reached consensus on a series of recommendations regarding hysteroscopic procedural technique and surgeon training in hysteroscopy. The panel intends to publish and publicize these recommendations in order to enhance understanding and appreciation of the risk of gas and room air embolism in hysteroscopic surgery, and thereby to reduce the potential associated morbidity and mortality.

GYNECARE anticipates incorporating all or some of these recommendations in its revised labeling for the VERSAPOINT system.

These recommendations arise from an understanding of the factors that predispose to gas and room air embolism during operative hysteroscopy in general. These factors can be segregated according to the mechanism by which gas/air enters the venous circulation, i.e., via an active mechanism (forced in by high intra-uterine pressure), or via a passive mechanism (sucked in along the pressure gradient generated by negative pleural pressure).

The predisposing factors are understood to be the following:

- 1) Predisposing factors in *active embolism* include:

- Use of high flow/pressure gas in the uterus, as in the gas-cooled sapphire tip YAG laser.
- Excessive intrauterine pressure.
- Access of air into uterus via non-purged lines, piston action of repeat instrument insertion, use of rigid fluid bottles.
- Presence of large venous channels, as with large myomas.
- Penetration into myometrium.
- Inadequate uterine flushing.
- Excessive operating times.

2) Predisposing factors in *passive embolism* include:

- Presence of large venous channels, as with large myomas and pregnancy.
- Disruption and exposure of vasculature.
- Patient position.
- Size of instruments.

Consensus Statement: Recommendations Regarding Hysteroscopy

The Panel recommends that the following principles be universally adopted:

- a. Operating room personnel must be trained to purge air from fluid lines prior to surgery, avoid entry of air into fluid lines and turn off pumps during bag changes, and to provide continuous, careful attention to fluid deficits.
- b. Basic equipment must be available to fulfill the requirements for monitoring of fluid deficit, assessment and control of intrauterine pressure and anesthesia monitoring.
- c. Surgical team must have access to appropriate resuscitative capabilities.
- d. Detection of room air and gas embolism mandates communication and collaboration between surgeon and anesthesiologist.
- e. The surgeon must be trained in the principles of hysteroscopic surgery including patient selection, technique, recognition and management of complications.
- f. Surgeon must employ good judgement in patient selection taking into consideration the size, number, type (i.e., Type I, II) and location of myomas.
- g. Surgeon should comply with guidelines for hysteroscopy published by AAGL and other international societies.

- h. Patients should be kept flat or in the reverse Trendelenberg position.
- i. If room air or gas embolism is suspected, surgeon should consider interrupting surgery, deflating the uterus and removing sources of fluid and gas until the diagnosis and a management plan are clarified.
- j. Surgeon should avoid entry of air into uterus by:
 - Carefully purging air from fluid in-flow lines and hysteroscopic devices prior to use.
 - Removing the weighted speculum as soon in the case as feasible in order to decrease exposure of the open cervix to room air.
 - Keeping the cervical os occluded during surgery as much as possible once it is dilated.
 - Using active fluid out-flow to effectively flush the uterus of bubbles and debris.
 - Using a Y-connector on the fluid in-flow line in order to reduce air entrainment during bag changes.
 - Minimizing the frequency of removal and reinsertion of hysteroscopic devices, and supplemental dilation of the cervix after initiation of the procedure.

Consensus Statement: Special Considerations for the Anesthesiologist

The panel recommends that anesthesiologists attending cases involving operative hysteroscopy consider the following:

- a. Anesthesiologists should be trained in the inherent risks of hysteroscopic surgery.
- b. Nitrous oxide anesthesia may enlarge the size of air bubbles, and thus should be avoided when possible in operative hysteroscopy.
- c. Patients at high risk for room air and gas embolism, as judged by the aforementioned factors, should be managed using controlled ventilation.
- d. For high risk patients undergoing operative hysteroscopy, consider intra-intra-operative monitoring, such as end-tidal CO₂ monitoring if under general anesthesia, and pre-cordial Doppler monitoring to detect room air and gas emboli early.

D. SCIENTIFIC INVESTIGATIONS AS PREREQUISITES TO RE-INTRODUCTION OF THE GYNECARE VERSAPOINT SYSTEM

Among the objectives of the Panel meeting was the review and appraisal of the research strategy proposed by GYNECARE as a prelude to market re-entry of the GYNECARE VERSAPOINT system. To this end, the Panel critically reviewed

the benchtop data generated during the last year as well as the individual research activities of the panelists. These data were interpreted in light of the assessment of the reported cases, the perceived risk of embolization in hysteroscopic surgery and the recent market withdrawal of the product.

Consensus Statement: In-vitro Data as Further Evidence

The Panel concluded that reinterpretation of the reported cases and recognition of the underlying risk of room air and gas embolism in hysteroscopic electrosurgery were alone insufficient to justify the re-introduction of the GYNECARE VERSAPOINT system to the market. Questions about device safety, once raised, need to be addressed with evidence.

Among the measurable parameters considered by the panel, the rate of gas production and composition of gases generated were judged to be the most relevant predictors of a device's contribution to clinically significant gas embolization.

The panel asserted that the critical objective of research studies is to establish the equivalence of the GYNECARE VERSAPOINT system and comparable monopolar devices in terms of gas production and gas composition.

Moreover, the panel concluded that the evidence needed to demonstrate equivalence between the GYNECARE VERSAPOINT system and monopolar devices can be obtained through in-vitro studies. Publishable, rigorously obtained data is required.

Animal and human studies are not necessary unless the gas production rate and/or composition are not equivalent.

Consensus Statement: Equivalence in Gas Composition

Upon review of gas characterization data obtained by Gyrus Medical, Ltd. and the National Physics Laboratory (Middlesex, UK), the Panel asserted that there was sufficient evidence to conclude that there was equivalence in gas composition (both gas identity and relative concentration) between the GYNECARE VERSAPOINT system and a comparable monopolar device.

The panel asserted that, except for a low percentage of Nitrogen (2.6%), all identified gas constituents are known to be highly soluble in blood.

The panel concluded that the gases produced by hysteroscopic electrosurgery would remain in gas phase (i.e., as bubbles in the bloodstream) for only a very brief time and would have limited clinical significance as a result.

The panel observed that the limited morbidity of the gas emboli in the reported cases is consistent with the small fraction of insoluble gases found in the gas composition data.

The Panel observed that room air emboli are more intrinsically dangerous due in part to the large component of insoluble Nitrogen in room air that leads to long-lived bubbles in the circulation. By corollary, the Panel speculated that events that are catastrophic are likely due to air emboli, rather than gas emboli, unless the latter are massive in volume and rapidly introduced into the circulation, improperly treated or neglected.

Consensus Statement: Equivalence in Gas Production

The panel critically reviewed gas production rate data generated by GYNECARE and observed equivalence in gas production per unit time between different GYNECARE VERSAPOINT electrodes. There was an apparent higher rate of gas production by comparable monopolar devices.

The panel observed that further assessment of the monopolar devices was warranted utilizing alternative generators in common usage and maximal power settings.

The panel reviewed data generated by Gyrus Medical, Ltd. and observed that the volume of gas produced per unit of tissue removed appeared higher with the Zero Degree Vaporizing electrode than with a comparable monopolar vaporizing electrode. The panel observed that the use of old morbid tissue in this study may have skewed the results since the monopolar electrodes' performance is more dependent upon tissue impedance than GYNECARE VERSAPOINT electrodes. Moreover, the panel observed that the estimates of volume-of-tissue-removed through use of weight-based measurements are subject to significant artifact induced by the desiccatory effect of monopolar electrodes. The panel suggested that further assessment of cc/gram be considered if these potential confounding artifacts can be overcome.

The panel concluded that, while preliminary data does suggest the gas production rates of the GYNECARE VERSAPOINT system is less than comparable monopolar devices, further investigation into gas production are required before definitive conclusions can be reached.

E. SUMMARY STATEMENT

Upon consideration of:

- **data presented to it by GYNECARE regarding the eight reported cases of gas embolism,**
- **in-vitro studies performed during the investigation into the potential association between the GYNECARE VERSAPOINT system and gas embolism,**
- **the state of current scientific knowledge, and**
- **the collective experience and expertise of its members**

The Panel concludes the following:

- 1) Of the eight cases reported to GYNECARE as gas or room air emboli, only three are likely to have been gas emboli potentially associated with activation of the electro-surgical device. The remaining cases likely involved room air or alternate physiological aberrations such as fluid overload not attributable to the operation of the electro-surgical device.**
- 2) Room air and gas emboli are associated with uterine surgical procedures, not specific devices.**
- 3) Complaint data alone does not allow for a valid comparison regarding the relative incidence or risk of gas and room air emboli in monopolar and bipolar hysteroscopic surgery.**
- 4) Re-introduction of the GYNECARE VERSAPOINT system to the market is justifiable, appropriate and acceptable if GYNECARE demonstrates with valid, publishable data that the gas production rate of the GYNECARE VERSAPOINT electrodes is equivalent to that of comparable monopolar devices.**
- 5) GYNECARE has already sufficiently demonstrated that the gas character is equivalent between said devices.**
- 6) There is need to further educate and warn hysteroscopists, anesthesiologists and operating room personnel about the risk of room air and gas emboli in general hysteroscopic surgery.**

The panel will convene in the future as necessary.

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