

**Research****Special Topic**

Contraceptive Vaginal Rings: Do They Pose an Increased Risk of Venous Thromboembolism in Aesthetic Surgery?

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Abstract

Nuvaring (Organon, Kenilworth, NJ) is a vaginal contraception ring inserted by the patient. It was approved by the Food and Drug Administration in 2001 for the prevention of pregnancy. The intent of this paper is to increase the awareness of Nuvaring among plastic surgeons, and to explore the risks associated with its use. We report the cases of two cosmetic surgery patients. These patients developed deep venous thrombosis and pulmonary emboli in the postoperative period while using Nuvaring. The very advantages of the Nuvaring—the ease of use, the avoidance of daily administration, and the insertion and removal of the device by the patient—may lead to the failure of patients to recollect being on a vaginal ring for contraception.

Level of Evidence: 4

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It is a common clinical scenario for an aesthetic plastic surgeon to treat a female patient seeking cosmetic surgery who is taking some form of contraception. In 2010, 62 million US women were in their child-bearing years (15–44) and 70% were at risk of unintended pregnancy.¹ In 2010, 2.2% of all contraceptive users in the US (830 000 of 61 million) used a vaginal ring as their method.¹ It is imperative that the plastic surgeon both uncover the use of contraceptives in their preoperative evaluation and have the patient stop contraceptives for at least 4 weeks before surgery. The surgeon can also advise the patient to seek alternative means of contraception (condoms, etc.) for both before and after surgery. The manufacturer's recommendation for Nuvaring, a vaginal ring, is to cease its use for at least 4 weeks before surgery and to not restart it until at least 2 weeks after surgery, as per the package insert Warnings and Precautions section (Merck & Co, Inc, last revised 11/2014). The purpose of stopping the oral contraceptive use before surgery is to avoid the increased risk of venous thromboembolism (VTE) among contraceptive users in the perioperative period.^{2–4}

Nuvaring (Organon, Kenilworth, NJ) is a vaginal contraception ring approved by the Food and Drug Administration in 2001 for the indication of prevention of pregnancy. It is a non-biodegradable, latex-free, flexible, transparent, combined contraceptive vaginal ring.⁵ The ring must be inserted by the patient in the vagina on or before day five of the menstrual cycle. Each ring is worn for 3 weeks, followed by a 1 week interval without the ring.⁶ After 7 days, the patient inserts a

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new ring. Each ring contains 2.7 mg of ethinylestradiol (EE) and 11.7 mg of etonogestrel, and releases on average 0.015 mg/day of EE and 0.120 mg/day of etonogestrel over a 3 week period of use.^{5,7} Etonogestrel is the active metabolite of desogestrel, a third-generation progestin and common component of oral contraceptive medications. It is the progestin component of oral contraceptives that have been most recently implicated in the increased risk of venous thromboembolism.^{2,8,9,10} Studies published in 1995 and 1996 demonstrated that third-generation progestins (desogestrel and etonogestrel) were associated with a higher risk of venous thrombosis in comparison to the older progestins (levonorgestrel and norgestrel).^{2,8,9,10} One study reported that the use of third-generation oral contraceptives was associated with a four-fold increase in the risk of venous thromboembolism compared to users of second-generation oral contraceptives, particularly among young, healthy women.^{3,11}

The vaginal ring's steady release of the EE and etonogestrel allows for continuous absorption through the vaginal epithelium. The systemic exposure to EE, the estrogen component, with the vaginal ring is about half the exposure to EE with the third-generation oral contraceptives.¹² The pharmacokinetics of etonogestrel, the progestin component in the vaginal ring, are different in comparison to oral contraceptives, with a lower overall dose given but a higher absolute bioavailability leading to a similar systemic exposure for both modalities of administration.¹³

The potential advantages of the vaginal ring in comparison to oral contraceptives include: ease of use and convenience; avoidance of daily administration, resulting in higher compliance and more effective contraception; constant lower plasma concentrations of the drugs; avoidance of gastrointestinal and hepatic first-pass metabolism; and insertion and removal of the device by the patient. In comparison to oral contraceptives, Nuvaring has been reported in the literature to offer better cycle control and a higher likelihood to continue with the contraceptive once using it.¹⁴

Despite these proven and potential advantages, Nuvaring is relatively new and data about its adverse effects are limited. Two cases of cerebral venous sinus thrombosis in healthy patients on Nuvaring, a relatively rare clinical entity, have been reported in the literature.^{15,16} A recent *New England Journal of Medicine* article suggested a higher adjusted relative risk of thrombotic stroke in patients who used a vaginal ring or a transdermal patch in comparison to patients on oral contraceptives. Although the higher adjusted relative risks were statistically indistinguishable and the confidence intervals overlapped, the authors went on to suggest that one might expect a higher risk of thrombotic stroke with parenteral administration than with oral administration of combined oral contraceptives.¹⁷

Nuvaring, designed to deliver a lower dose of hormones in comparison to oral contraceptives, is hypothesized to lower the risk of venous thrombosis due to the lower exposure to

hormones. Although the data is still limited, recent studies have begun to call this hypothesis into question. One study found higher levels of activated protein C resistance and sex hormone-binding globulin—both measures associated with an increased risk of venous thrombosis—in patients on the vaginal ring in comparison to those on second-generation oral contraceptives.¹⁸ The authors went on to state that third-generation combined contraceptives have a higher prothrombotic effect than second-generation ones, independent of the route of administration.¹⁸ Five cases of deep vein thrombosis (DVT) associated with Nuvaring have been reported in the literature.¹⁹⁻²³ These reported cases were in healthy patients on Nuvaring with no other risk factors for DVT and no recent surgeries. We report two cosmetic surgery patients from two different surgeons who developed DVTs and pulmonary emboli in the postoperative period while taking Nuvaring.

CASE 1

A healthy 26-year-old African-American female presented to the first surgeon's clinic in May 2011 for breast augmentation. Her medical and surgical history was only notable for asthma, for which she was not on any medications. The patient denied a history of VTE or cancer or any recent immobility, trauma, surgery, pregnancy, or miscarriages. She also denied taking any medications or contraceptives, both on the patient intake form as well as in the patient interview. She reported no drug allergies or any history of smoking, alcohol, or illicit drug use. She reported no family history of any diseases or hypercoagulation disorders. There were no clinical abnormalities on physical examination. The patient had a pre-treatment history and physical examination and pre-treatment clearance by her primary care doctor, as well as pre-treatment labs [complete blood count (CBC), Chem-7, prothrombin time/partial thromboplastin time (PT/PTT), urine pregnancy test, and EKG] that were all normal. She was scheduled for a bilateral breast augmentation.

Given the patient's absence of known risk factors for DVT, she was assessed as moderate risk for DVT because of the 1 hour surgery planned, and intermittent pneumatic compression stockings were used for DVT prophylaxis. She underwent placement of bilateral, subglandular, smooth, round-profile silicone gel implants (286 cc Allergan style 15) under general anesthesia. The surgery was uneventful. The patient was seen on postoperative day 2 and was doing well and had no complaints. On postoperative day 12, the patient contacted the office because of right-sided chest pain. The patient was brought back to the clinic for immediate evaluation. The patient did report a history of right-sided calf pain that presented on postoperative day 2 and spontaneously resolved two days later. She now described deep right-sided chest pain, which worsened with full

inspiration. Her vital signs were a pulse of 100, respiratory rate of 20%, and 100% saturation on room air on pulse oximetry. She had good breath sounds bilaterally on auscultation. Examination of the lower extremities did not reveal any significant swelling, cyanosis, or calf tenderness, and bilateral Homan's signs were negative.

The patient was transferred via ambulance to the emergency department for workup for a suspected pulmonary embolism. Initial labs with coagulation profile (PT, PTT) and CBC were normal. A chest x-ray done in the emergency department was unremarkable. A spiral CT scan revealed bilateral pleural effusions and filling defects in segmental branches of the pulmonary artery in the left upper and lower lobes and the right lower lobe, consistent with bilateral pulmonary emboli (Figure 1). The spiral CT scan also demonstrated a deep vein thrombosis in the distal right superficial femoral vein, popliteal vein, and veins of the right calf (Figure 1).

The patient was admitted to the medical service for management of pulmonary emboli and deep vein thrombosis. She was started on therapeutic enoxaparin (90 mg) subcutaneously daily and then, a day later, began a daily warfarin regimen. After discovering that the patient was on Nuvaring implantable contraception, it was stopped. During the

hospitalization, a workup for hypercoagulability disorders, including Factor V, was negative. She was discharged on hospital day 3 on an anti-coagulant program, with instructions to follow up with hematology. The patient completed 5 months of warfarin therapy and was advised to permanently avoid hormonal-based contraceptives. She was seen in follow-up at just over 7 months postoperative, when she was free of symptoms and doing well from an aesthetic standpoint.

CASE 2

A healthy 29-year-old non-smoking Caucasian female presented to the second surgeon's office in June 2011 for an abdominoplasty. The patient's past medical history was significant for non-Hodgkin's lymphoma of the chest, diagnosed 8 years prior and treated with chemotherapy. She had been free of disease for 5 years. The patient denied a history of VTE or any recent immobility, trauma, surgery, pregnancy, or miscarriages. She also denied taking any medications or contraceptives on both the patient intake form as well as in the patient interview. She reported no drug allergies or any history of smoking, alcohol, or illicit drug use. She reported no family history of any diseases or hypercoagulation

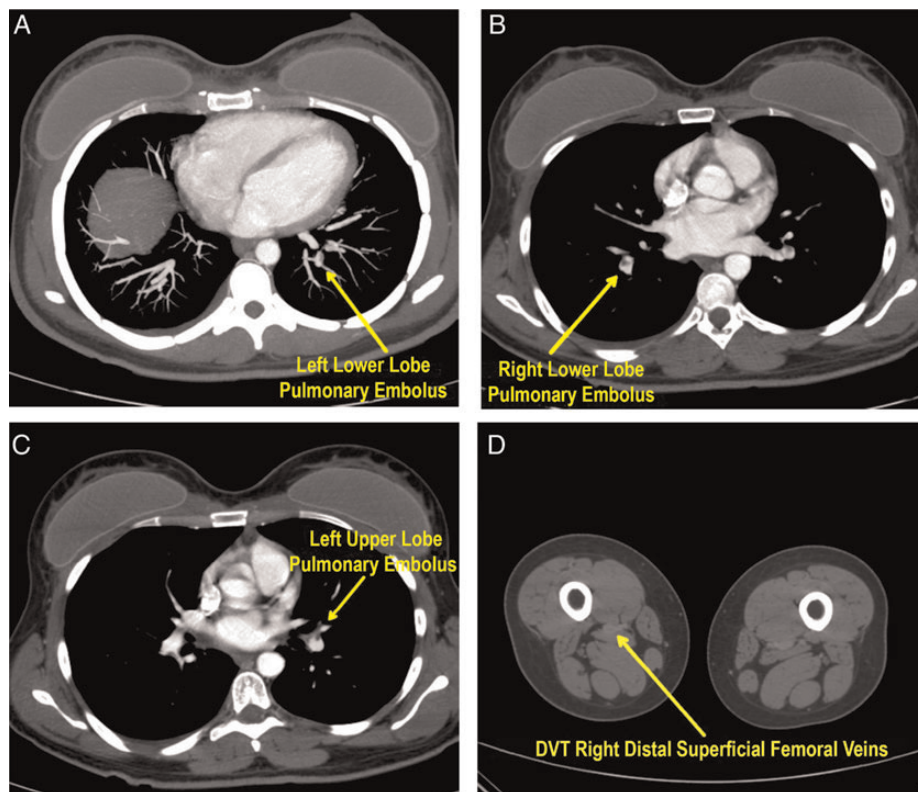


Figure 1. CT images of the chest and lower extremities of a 26-year-old woman demonstrating the following: (A) left lower lobe pulmonary embolus as denoted by the arrow, (B) right lower lobe pulmonary embolus as denoted by the arrow, (C) left upper lobe pulmonary embolus as denoted by the arrow, and (D) deep vein thrombosis (DVT) of the right distal superficial femoral vein.

disorders. The patient had a preoperative history and physical examination and preoperative clearance by her primary care doctor, as well as preoperative labs (CBC, Chem-7, PT/PTT, Urine Pregnancy, EKG) that were all normal.

The patient underwent an abdominoplasty without plication for 3 hours under epidural anesthesia without any complications, and was discharged to home on the day of surgery. Intermittent pneumatic compression devices and elastic stockings were used for DVT prophylaxis during the surgery.

On postoperative day 5, the patient presented via ambulance to the emergency department in no acute distress but complaining of increased weakness, fatigue, and dizziness. She also noted palpitations and chest discomfort but no shortness of breath. She was tachycardic (120 beats/seconds) and mildly hypotensive (90/55), but had a pulse oximetry saturation of 95% on room air. She had bilateral breath sounds, and examination of her lower extremities was normal.

The patient was given maintenance intravenous fluids and boluses for her suspected dehydration from poor oral intake in the relatively immediate postoperative period. A 12-lead electrocardiogram demonstrated sinus tachycardia with a T-wave abnormality. Lab work was essentially normal, except for a slightly elevated white blood cell count of 12.2 and mild anemia with a Hemoglobin of 9.6 and a Hematocrit of 27.7. There was strong consideration for pulmonary embolism given her clinical presentation and the recent abdominoplasty.

CT angiography of the chest was ordered, which confirmed massive bilateral pulmonary emboli with involvement of segmental and subsegmental branches of the pulmonary artery system, as well as dependent bibasilar atelectasis (Figure 2). Evidence on the CT scan of slight bowing of the interventricular septum was noted, which suggested right heart strain. The abdomen and pelvis were negative on the scan, except for the presence of a contraceptive ring device in the upper vagina and a small amount of pelvic ascites. No evidence of any obvious deep venous thrombosis was detected on the CT scan.

The patient was questioned about the contraceptive ring device, and disclosed at this time that she was on a Nuvaring contraceptive device at the time of the surgery, and had been on the device for some time. According to the patient, she had denied any medications in all of her preoperative workup because she forgot she was on Nuvaring. After the diagnosis of pulmonary embolism was confirmed, weight-based heparin therapy was started with a bolus and maintenance drip. Vascular surgery was consulted for a potential embolectomy, and the patient was admitted to the intensive care unit.

Transthoracic echocardiography was performed and showed normal left ventricle size and function, but a dilated right ventricle with moderately reduced right ventricular function. The echocardiogram also revealed evidence of systolic pulmonary hypertension. Venous dopplers of bilateral

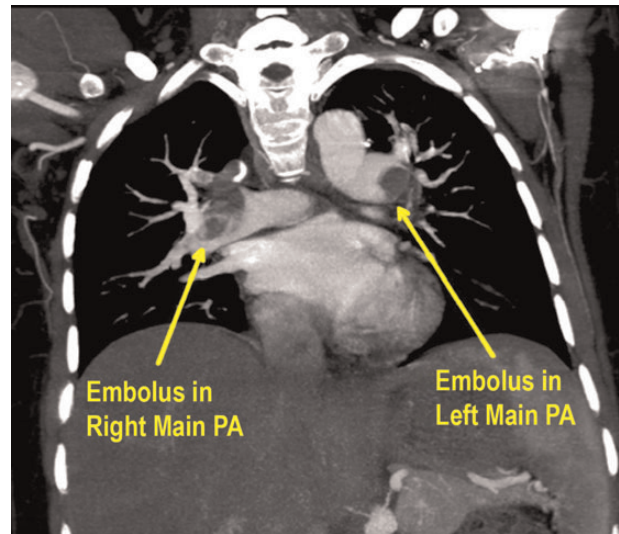


Figure 2. CT angiography of the chest image of a 29-year-old woman demonstrating bilateral pulmonary emboli in both main pulmonary arteries (PA).

lower extremities were also done and showed a deep venous thrombosis in the left common femoral vein.

Vascular surgery was recommended for therapeutic benefit as well as to minimize possible future complications such as pulmonary hypertension and right heart strain. On hospital day 2, the patient received a pulmonary angiography with catheter embolectomy of bilateral pulmonary emboli using the AngioJet Xpedior system (Bayer HealthCare, Indianola, PA). An angiogram demonstrated a filling defect of the right main pulmonary artery and the left pulmonary artery supplying the lower lobe (Figure 3). An embolectomy was done with full resolution of the clot in the right main pulmonary artery and a majority resolution in the left pulmonary artery.

The patient recovered and heparin therapy was transitioned to enoxaparin (65 mg subcutaneous every 12 hours) and warfarin. She was maintained on enoxaparin until adequate anticoagulation could be achieved with the warfarin regimen. During her hospital course, she remained stable with normalization of her tachycardia and she was discharged on warfarin with a therapeutic international normalized ratio (INR) level on hospital day 8, with instructions for follow-up. No primary hypercoagulability disorders were detected on hematologic workup as an outpatient. The patient completed a 6 month course of warfarin, and had no further incidents related to the pulmonary embolism. She was advised to avoid all hormonally-based birth control methods.

DISCUSSION

We have reported two cases of VTE in patients who were on Nuvaring and did not disclose that fact to the operating

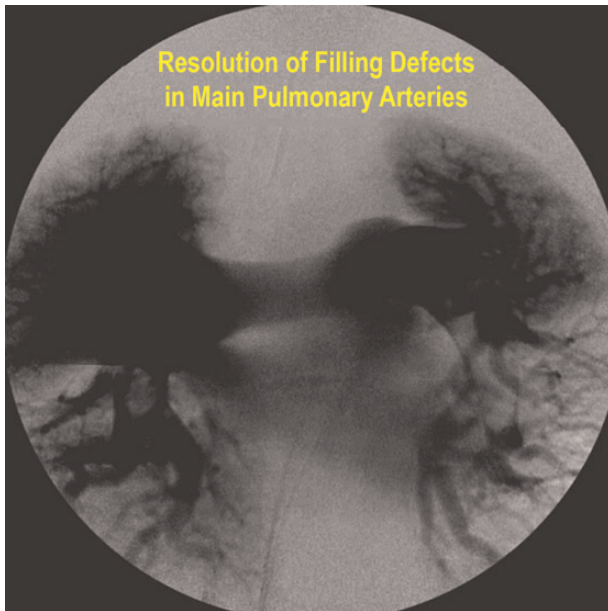


Figure 3. Intraoperative pulmonary angiography of a 29-year-old woman with resolution of the pulmonary artery filling defects after catheter embolectomy of bilateral pulmonary emboli using the AngioJet Xpeedior system.

surgeons before their cosmetic surgeries. In both cases, the patients denied taking any medications, both on their patient intake forms as well as in their patient interviews. The very advantages of the Nuvaring—the ease of use, the avoidance of daily administration, and the insertion and removal of the device by the patient—may be the very reason that leads to the failure of patients to disclose being on a vaginal ring for contraception. Patients may not consider that a vaginal ring is a medication that needs to be reported to the physician. Given the fact that the patient population that has cosmetic surgery often uses some form of contraception, plastic surgeons may encounter more patients using Nuvaring in the future. It is imperative that plastic surgeons are aware of the existence of the Nuvaring device so that they can determine if a patient is using it and discontinue its use before surgery. Plastic surgeons should specifically ask patients if they are using a vaginal ring in their risk evaluation for VTE.

Venous thrombembolism is a significant source of postoperative morbidity and mortality in postoperative surgical patients. A British Medical Journal study points out a 10 time increased risk of VTE in female middle-aged women having day surgery than those not having surgery. This risk increases to 70 times more likely in patients having inpatient surgery and persists for up to 12 weeks after surgery.⁴ None of the five cases of DVT associated with Nuvaring reported in the literature were in postoperative patients.¹⁹⁻²³ Clearly, both of the patients reported above were at increased risk just from having surgery, but the degree of the

additional risk that can be attributed to Nuvaring in these cases is unknown.

To explore the question of the additional risk attributed to the Nuvaring, we retrospectively assessed each patient's preoperative risk for VTE using the Caprini risk score. The Caprini risk scoring system takes into account most known risk factors for the development of VTE and assigns each patient a score based on the presence or absence of these factors.²⁴ The largest study demonstrating the value of the Caprini risk scoring system involved 8216 surgical patients as part of the National Surgical Quality Improvement Program.²⁵ The authors classified the patients into four groups, based on their assessment scores, and calculated the associated incidence of VTE: a low risk score of 0–1 corresponded to a VTE incidence of 0%; moderate risk score of 2 to a VTE incidence of 0.7%; a high risk score of 3–4 with a VTE incidence of 0.97%; and the highest risk score of 5–9+ with a VTE incidence of 1.33–6.51%. As expected, the incidence of VTE increased as the risk score increased.²⁵ In terms of references specific to the plastic surgery population, the Venous Thromboembolism Prevention Study (VTEPS) is the largest study to date that examines a risk-stratified approach to chemoprophylaxis. A recent publication based on the VTEPS data demonstrated that the 2005 Caprini Risk Assessment Model provided superior risk stratification in comparison to the 2010 Model.²⁶

The Caprini scoring system adds one point to the patient's overall risk score for VTE for the use of oral contraceptives or hormone replacement therapy, and two to five points for major surgery, depending on the length of the surgery. These two risk factors alone can place a patient into the high-risk category for VTE. Some plastic surgeons consider having an abdominoplasty as a separate risk factor, assigning it five points in the Caprini scoring system and automatically elevating those patients to a high-risk category, indicating the need for chemoprophylaxis in those patients.²⁷ Using the Caprini scoring system, the patient in case 1 would have been classified as high risk based on her pretreatment risk score of three: one point for the use of contraceptives and two points for the 1 hour major surgery. With the non-disclosure of the use of the Nuvaring, the patient's risk score decreased to two, putting her in the moderate risk category. Intermittent pneumatic compression stockings were used for VTE prophylaxis given the patient's moderate risk assessment. With better awareness of the Nuvaring, the operating surgeon may have been able to elicit the presence of the vaginal ring in the patient, discontinue its use, and place the patient on the appropriate chemoprophylaxis regimen for VTE prevention given her high-risk assessment.

As mentioned above, the Caprini risk assessment assesses one point for the use of oral contraceptives or hormone replacement therapy when calculating a risk score. Does Nuvaring pose the same risk for VTE in surgical patients as third-generation oral contraceptives, or is there an increased

risk? Should the risk assessment be different for Nuvaring? The answer to these questions are unknown, but two studies mentioned in the introduction have suggested an increased risk of thrombotic stroke and increased levels of activated protein C resistance with Nuvaring in comparison to oral contraceptives.^{17,18} It is also important to note that these are the first two reported cases of VTE in postoperative patients on Nuvaring. All of the previously-reported cases of VTE in patients on Nuvaring have been in non-surgical patients. No data are available about the risk of venous thrombosis of the vaginal ring in comparison to third-generation oral contraceptives. Given the fact that a large portion of patients having plastic surgery are candidates for Nuvaring, further studies are needed to explore these questions.

In case 2, the patient was already at the highest risk of VTE according to the Caprini risk assessment, but was not given chemoprophylaxis by the operating surgeons. The patient had a major surgery lasting 3 hours (three points), a history of previous malignancy (two points), and was on a Nuvaring at the time of surgery (one point). This gives the patient a total risk score of six, placing her in the highest risk class for VTE. The operating surgeons decided not to use chemoprophylaxis in this case because it was done under epidural anesthesia. The Caprini risk assessment does not specify whether or not the ongoing use of contraceptives during surgery constitutes an increased risk for VTE. It also only includes the use of oral contraceptives in its risk assessment score, not vaginal rings or transdermal patches. As we learn more about the effects of Nuvaring, the risk assessment may need to be adjusted to account for nuances specific to the vaginal ring.

The pharmacokinetics of the vaginal ring are different in two important ways that may pose an increased risk for VTE. The first difference, as mentioned in the introduction, is avoidance of gastrointestinal and hepatic first-pass metabolism. It does seem anatomically plausible that a venous system exposed to the drainage from the vaginal epithelium would have higher serum levels of hormone exposure before it reaches the liver, increasing the potential for VTE. The second difference is the maintenance of constant serum levels of hormones. As noted in the paper by van den Heuvel et al,¹³ the hormone serum levels have very little variation with the vaginal ring. The oral contraceptives have more variability, with more peaks and troughs in their serum levels. The constant serum levels of patients on the vaginal ring are higher than the trough serum levels of the patients on oral contraceptives. This leads to a more constant higher exposure to hormones.¹² We point out these pharmacokinetic differences between the two modalities of treatment but have no data as to the clinical implications of these differences.

In case 2, the Nuvaring was discovered only after the patient developed a VTE and the vaginal ring was seen on the CT scan. If the patient in case 2 had disclosed the use of a Nuvaring before surgery, the surgery could have been

delayed for 3–4 weeks to allow the patient to discontinue use of the vaginal ring. The question remains whether Nuvaring should be restarted 2 weeks after surgery if the patient is ambulatory, as is recommended with oral contraceptives. The recommendations and risk assessments related to the Nuvaring have been given under the premise that they are the same as oral contraceptives. The authors of this paper question this premise until further studies explore the true risks related to the use of the Nuvaring in surgical patients. This study is limited by its small patient population of two and is not intended to provide statistical evidence in regards to the risks of vaginal rings. It is the intent of the authors to educate the plastic surgery community about vaginal rings and to begin further studies into the potential VTE risks associated with their use.

CONCLUSION

We report two cases of venous thromboembolism in patients having aesthetic surgery while on Nuvaring. The authors recommend that until the exact potential risk of VTE associated with Nuvaring is elucidated, surgeons should specifically query aesthetic surgery patients as to its use and discontinue its use from 4 weeks preoperatively to 2 weeks postoperatively.

Disclosures

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