Stroke and Etonogestrel/Ethinyl Estradiol Ring (NuvaRing): Clinical, Radiological, and Prognostic Features

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Background: A recent study found that NuvaRing (a vaginal contraceptive ring containing 15 μg ethinyl estradiol and 120 μg etonogestrel) has 2.5 times increased relative risk of thrombotic stroke compared to nonuse. *Objective:* We studied a case series of 19 such patients as well as prior published case reports to clarify clinical, radiological, and prognostic features. *Methods:* Medical records and imaging for 18 cases were initially systematically reviewed for consultation in a class action lawsuit. One case was seen personally outside of litigation. All 19 cases were entered into a database detailing clinical, radiological, and prognostic features as well as other potential risk factors. A literature search identified 8 additional cases. *Results:* Average age at stroke was 31.7 ± 9.8 years; average duration of NuvaRing use prior to stroke was 11.2 months. Arterial stroke occurred in 10 of 19 (52%); 1 of 10 (10%) was hemorrhagic. Venous sinus thrombosis was present in 11 of 19 (58%) on initial imaging; 6 of 11 (54%) were hemorrhagic. The most common presenting symptom was headache (7 of 19 [37%]) and motor weakness (7 of 19 [37%]). A hypercoagulable condition was present in 3 of 19 (16%); 3 of 19 (16%) had history of hypercoagulable disease in a first-degree relative. Mortality was .5%; 8 of 19 (42%) fully recovered and 3 of 19 (15%) were discharged to rehabilitation. *Conclusions:* In this largest case series of NuvaRing-associated stroke to date, approximately half of the strokes are venous and half are arterial. Stroke typically occurred within the first year of use, and as soon as 2 weeks after NuvaRing initiation. **Key Words:** Stroke—NuvaRing—contraceptives—hypercoagulable—cerebral venous thrombosis—stroke in young.

Introduction

Combined oral contraceptives (COCs) have been used for ovulation inhibition since the 1960s. Sixty-two percent of 12,279 U.S. women aged 15-44 stated that they use some form of contraception in a survey conducted by the Centers for Disease Control and Prevention from 2006 to 2010.[1] Of the users, 28% used oral contraceptives (OCPs) in 2010 (compared to 27% in 2006) and 7.2% used other hormonal contraceptives in 2010 (compared to 4.3% in 2006, a 75% increase). The risk of thromboembolism with use of hormonal contraceptives, both oral and nonoral, has been established. It is a risk that clinicians and women have to weigh before deciding which form of contraception is the best option.

NuvaRing is an approximately 5.5 cm diameter plastic (an ethylene-vinyl co-polymer) ring that delivers 120 μg of etonogestrel, a third-generation steroidal progestin, and 15 μg of estradiol, a steroidal estrogen, per day. It is vaginally inserted and maintained for 1 month then replaced.

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Data regarding nationwide usage are not available, but in 2010, approximately 5.5 million prescriptions were written for the device. Theoretically it could have less risk of stroke or thromboembolism than COCs because it contains less ethynlestradiol (EE) than COCs (typically 30 μg) and also the hormones are absorbed by the vaginal mucosa and act systemically bypassing liver first-pass metabolism where coagulation factors are synthesized.[2] However, the relative risk of venous thrombosis with use of non-OCPs (depot injections, transdermal patches, and transvaginal devices) has been shown to be 7.9 times the relative risk in nonusers of hormonal contraceptives[3] and two times the risk in users of corresponding COCs,[4-6] although not all studies have found an increased risk.[7,8]

We present 19 cases of stroke, including both arterial and venous thrombosis, along with clinical, neuroimaging, and prognostic characteristics. We also investigate available serological data to determine any correlation with proposed theories of the thrombotic properties of steroid hormones. Our systematic literature search identified 8 other reported cases of stroke in NuvaRing users,[2,9-12] and these cases are summarized as well.

Materials and Methods

This retrospective case series and systematic literature review was approved by SUNY Downstate Institutional Review Board. Eighteen case records, all between 2006 and 2007, were from NuvaRing class-action litigation. Information about study subjects was kept anonymous and confidential, and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996. One additional case was seen personally by the author (S.R.L.) in 2009. A PRISMA-based, systematic literature search of PubMed was conducted in both March 2016 and September 2016 with search terms "Nuvaring," "Nuvaring and stroke," "Etonogestrel/Ethinyl Estradiol Ring," and "stroke" to identify previously published cases. References of all published cases were also reviewed.

Results

Clinical Features

The patients' clinical characteristics are summarized in Table 1. The women's ages ranged from 14 to 48 years with an average of 31.7 ± 9.8 years. The presenting complaint was headache in 7 (36.8%) of the cases.[3-5,7,10,13,14] Four cases (21.0%) presented with seizure (cases 8, 13, 14, and 17). Seven cases (36.8%) presented with motor weakness (cases 1, 2, 6, 10, 12, 15, and 18). At the time of stroke, the duration of NuvaRing use ranged from .75 to 36 months with average of 11.2 ± 11.1. Five of the cases (26.3%) were concurrently using another form of hormonal contraception (cases 4, 8, 9, 16, and 18). A predisposing hypercoagulable condition was present in 3 cases. Case 8 had both Factor V Leiden mutation and the C677T MTHFR mutation; case 16 had both lupus anticoagulant and heterozygote MTHFR A1298C mutation; and case 17 had antiphospholipid syndrome (Table 2).

Radiological Features

Of the 19 total cases presented here, cerebral and vascular imaging concluded that 11 cases (57.9%) were primary cerebral venous thrombosis (cases 3, 4, 5, 8, 9, 11, 13, 14, 16, 17, and 19), 7 cases (36.8%) were confirmed acute ischemic strokes (cases 2, 6, 7, 10, 12, 15, and 18), and 1 case was primary intracerebral hemorrhage (case 1).

The features of the cerebral venous thromboses varied by location, size, and effect. Four cases (21%) only involved 1 cerebral vein (cases 8, 13, 17, and 19). Cases 8 and 17 had single lesions in the transverse sinus whereas the 2 had the sigmoid and superior sagittal sinuses affected. There were 5 cases (26.3%) where 2 sinuses were affected (cases 4, 5, 9, 14, and 16). Only case 9 did not involve the superior sagittal or transverse sinus in the 2 sinus thrombosis groups. That patient had thrombosis of the internal cerebral veins and the vein of Galen. Multivessel thrombosis occurred in 2 cases (cases 3 and 11). These patients had extensive thromboses affecting both superior sagittal and transverse sinuses plus the vein of Galen in case 3 and the inferior sinus in case 11.

The effect of the cerebral venous thrombosis also varied among the presented cases. Six cases (31%) had hemorrhagic infarcts (cases 3, 5, 8, 9, 13, and 16). The hemorrhages occurred in the region of the draining sinuses. Case 3 had adjacent subdural and subarachnoid hemorrhages. Three cases (15.7%) had cerebral edema without infarction (cases 14, 17, and 19). Two cases had no parenchymal effects seen on neuroimaging (cases 4 and 11).

The features of the acute ischemic strokes varied by location and type. Four cases affected large vessels (cases 2, 7, 11, and 15) and 3 cases affected small vessels (cases 6, 12, and 18). Three cases had confirmed large vessel occlusion on vascular imaging. Case 2 had occlusion of the proximal left middle cerebral artery (MCA), case 11 had slowing of the distal L internal cerebral artery (ICA), and case 15 had hyperdense left MCA sign. Case 7 is consistent with infarction of the right superior cerebellar artery. The 3 cases involving small vessels all involved the brainstem—cases 6 and 18 in the pons and case 12 in the right lateral medulla. None of the ischemic strokes showed any evidence of hemorrhagic transformation.

One case had primary intracerebral hemorrhage without evidence of ischemic stroke or cerebral venous thrombosis (case 1). This patient had a large parenchymal hemorrhage in the left frontoparietal subcortical white matter extending into the basal ganglia. There was no intraventricular extension. The location of the hemor-