



OBJECTIVE

NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) was introduced in 2003 as a contraceptive. It has the safety profile of oral hormonal combined contraceptives (COC). Adverse effects on the liver are considered rare [1]. Gilbert's syndrome is a congenital disorder characterized by impaired glucuronyltransferase activity. It is defined by chronic elevated non-conjugated bilirubinemia with symptoms limited to fluctuating mild jaundice. We present a case of a drug-induced hepatitis in a patient with Gilbert's syndrome.

Percentage of woman reporting adverse events with NuvaRing and a COC in two non-comparative studies and three randomized controlled trials

Adverse event	Method	NuvaRing [n=2322] (Europe [3]-America [4])	NuvaRing [n=512] vs 150LNG/30EE COC [n=484] [5]	NuvaRing [n=499] vs DRSP/30EE COC [n=484] [6]	NuvaRing [n=94] vs 100LNG/20EE COC [n=94] [7]	NuvaRing [n=94] vs 60GES/15EE COC [n=92] [7]
Breast tenderness	NuvaRing	2.6 (1.9-3.3)	3.1	3.2	4.2	4.2
	COC		1.3	4.7	6.3	6.5
Headache	NuvaRing	5.8 (6.6-5.0)	7.2	6.8	6.3	6.3
	COC		5.8	7.6	9.5	9.7
Nausea	NuvaRing	3.2 (2.8-3.6)	2.7	0.8	2.1	2.1
	COC		4.0	3.7	7.4	5.4
Leukorrhea	NuvaRing	4.8 (5.3-4.2)	3.5	3.2	-	-
	COC		0.2	1.0	-	-
Vaginal discomfort	NuvaRing	2.4 (2.2-2.6)	-	1.4	-	-
	COC		-	0.0	-	-
Vaginitis	NuvaRing	5.6 (5.0-6.2)	3.9	4.6	-	-
	COC		1.0	2.1	-	-
Ring-related events [1]	NuvaRing	4.4 (3.8-5.0)	4.7	6.6	-	-
	COC		0.0	0.4 [2]	-	-

[1] Ring-related adverse events comprise foreign body sensation, coital problems, and expulsions.
 [2] dyspareunia.
 [3] Roumen et al 2001.
 [4] Dieben et al 2002.
 [5] Oddsson et al 2005a.
 [6] Ahrendt et al 2006.
 [7] Sabatini and Cagiano 2006.

Abbreviations: COCs, combined oral contraceptives; DRSP, drospirenone; EE, ethinyl estradiol; GES, gestodene; LNG, levonorgestrel.



CASE REPORT

A female patient presented to her general practitioner (GP) with complaints of icterus, high concentrations of bilirubin, elevated liver enzymes (AST 300 U/L) and localized eruption on the fingers. She reported recent repeated skin contact with Clean Tabs®, a medical device used to clean braces and/or dentures. The GP contacted the Belgian Poison Centre to discuss a possible link between her symptoms and the Clean Tabs® exposure. He had ruled out medication, herbal medicine, food supplementation and alcohol as possible causes. Serum serology tests had all been negative. Although the skin irritation could easily be explained by the composition of Clean Tabs®, it could not be linked to the liver symptoms. Further anamnesis about the patient's medication revealed that she had been using NuvaRing® as a contraceptive for 6 months. A liver biopsy was performed and showed a drug-induced hepatitis.

Treatment with NuvaRing® was stopped and liver enzymes normalized within two weeks. The patient was later diagnosed with Gilbert's syndrome, which explained her bilirubinemia, but not the abnormal liver enzyme values.

The patient restarted NuvaRing® 8 months later. A first blood test after 3 weeks' use revealed no hepatic abnormalities. Shortly thereafter, the patient stopped using NuvaRing® because of local discomfort. Given the short rechallenge period, this case report remains inconclusive.

CONCLUSION

We report a case of a drug-induced hepatitis in a patient with Gilbert's syndrome using NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) as a contraceptive. NuvaRing® and COC have a similar ADR profile [2]. Although the patients' symptoms resolved after stopping NuvaRing®, given the short rechallenge period no causal link could be formally established.

REFERENCES

- [1] Roumen FJME. Review of the combined contraceptive vaginal ring, Nuvaring®. Ther Clin Risk Manag. 2008;4:441-451.
- [2] Nguyen BT, Jensen JT. Evaluating the efficacy and safety of a progestin- and estrogen-releasing ethylene vinyl acetate copolymer contraceptive vaginal ring. Expert Opin Drug Saf. 2014;13:1423-30.

