

Difference between drospirenone-containing oral contraceptives and other oral contraceptives related to risk of venous thromboembolism

We wish to comment on the Dinger and Shapiro commentary article published in the January 2012 issue of this Journal.¹

Following the publication of papers regarding the risk of venous

thromboembolism (VTE) with combined oral contraceptives (COCs) we would like to share some information regarding comparison between drospirenone-containing COCs and other COCs in Croatia. This short study was conducted during the 3-year period 2008–2010 using data on drug utilisation and data on side effects from the Agency for Medicinal Products and Medical Devices of Croatia (HALMED). The total female population aged 15–49 years was about 1 050 000. Like other COCs in Croatia, drospirenone/ethinylestradiol (DRSP/EE) is issued on private prescription in pharmacies. They are usually prescribed by gynaecologists, but may also be prescribed by other specialists. The DRSP-containing COC, Yasmin®, existed in the Croatian market from 2005, but the new DRSP-containing COC, Yaz®, was introduced in 2010.

Total consumption of COCs in the 3-year period 2008–2010 amounted to 1 274 745 strips of tablets, 504 107 (39.5%) DRSP-containing COCs and 770 638 (60.5%) other COCs (Table 1). Assuming that, with negligible exceptions, the women concerned used their contraceptives regularly during the whole year (corresponding to 13 'pill-driven' cycles) their number would have been 38 778 for DRSP-containing COCs and 59 280 for other COCs.

We collected data on the COC prescription rate in Croatia and assessed whether there might be a link with the incidence of VTE. During that period the HALMED recorded 138 side effects and

Table 1 Consumption of oral contraceptives in Croatia during the period 2008–2010

Substance	Trade name	Consumption [n (%)]
Ethinylestradiol/norgestimate	Cilest®	196 670 (15.43)
Ethinylestradiol/gestodene	Logest®	237 750 (18.65)
Ethinylestradiol/levonorgestrel	Stediril®	293 (0.02)
Ethinylestradiol/norethisterone	Trinovum®	116 785 (9.16)
Ethinylestradiol/levonorgestrel	Triquilar®	219 140 (17.19)
Ethinylestradiol/drospirenone	Yasmin®	479 840 (37.64)
Ethinylestradiol/drospirenone	Yaz®	24 267 (1.90)
Total		1 274 745 (100.0)

Table 2 Thrombosis and embolism as side effects, substances and outcomes when applying oral contraceptives

Substance	Trade name	Outcome* and side effect†									
		1		2		3		4		5	
		T	E	T	E	T	E	T	E	T	E
Ethinylestradiol/drospirenone	Yasmin®	1	3	1		1	7	2	1	10	6
Ethinylestradiol/drospirenone	Yaz®		1								1
Ethinylestradiol/norgestimate	Cilest®					1	1			1	1
Ethinylestradiol/gestodene	Logest®						1	1		1	1
Total		1	4	1		2	9	3	1	12	9

*Outcome: 1, recovered/resolved; 2, not recovered/not resolved; 3, fatal due to reaction; 4, unknown; 5, missing data considering outcome.

†Side-effect: E, embolism; T, thrombosis.

complications related to the use of the COCs in the whole of Croatia.

Among these reports of side effects and complications there were 11 cases of verified VTE (including deep vein thromboses, cerebral venous thrombosis, thrombophlebitis superficialis and basilar artery thrombosis), nine cases of pulmonary embolism and one case of thrombosis and pulmonary embolism together, whereas the other reports referred to symptoms such as headache (10), nausea (7), muscle spasm (4), and so on.

For women who used DRSP-containing COCs, 17 side effects of thrombosis and pulmonary embolism were registered (0.438 per 1000 women), whereas for women who used other COCs only four side effects were noted (0.068 per 1000 women), which is 6.4-fold less. Thrombosis and embolism as side effects, substances and outcomes when taking various COCs are shown in Table 2.

However, in over half the cases ($n=12$) the outcome of thromboembolic complications remained unknown. Recovery was reported in five cases but, as already mentioned, there were two lethal outcomes where a direct causal relationship with the use of COCs could not be determined. We just determined a great difference in rate between these two groups. We can not establish a direct correlation between COC and side effect, but the difference in rates between DRSP-containing COCs and other COCs is fairly great.

Our results should be interpreted very cautiously, especially the 6.4-fold difference found, as our study has great limitations, such as not controlling for confounding variables such as age, weight, smoking, diabetes, prolonged immobilisation, pregnancy, having undergone a surgical procedure, having been subjected to major trauma, cancer, heart failure, family history of VTE, history of contraception, likelihood of biased VTE diagnosis conditional on DRSP use, time from start to event, and so on.

Confounding can never be excluded with certainty in observational studies; it seems that the biases that have been suggested and examined are not sufficient to account for the results.² A survey of medical records of hospitalised women and deaths could determine neither the exact causes nor the outcomes in most cases of VTE. We carefully studied the problems regarding analysis and re-analysis in the Dinger and Shapiro commentary,¹ and because we experienced very similar problems we agree with their claim that the increased risk of VTE among COC users is a class effect.¹

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References

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- 2 **Kemmeren JM**, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ* 2001;**323**:131–134.