

Clin-IQ Project

Clinical Question: In women over 35 years of age who smoke, does Mirena (levonorgestrel-releasing intrauterine system) reduce the risk of DVTs compared to oral contraceptives?

Authors: Melanie Marshall, MD (PGY-3) and Kristen Jordan, MD (PGY-2)

Faculty Mentor: James L. Brand, MD

Residency Program: University of Oklahoma Health Sciences Center, Department of Family and Preventive Medicine, Oklahoma City, OK.

Answer: Yes

Level of Evidence for the Answer: B

Search Terms: intrauterine device, venous thrombosis, oral contraceptives

Date Search was Conducted: September 2012

Inclusion and Exclusion Criteria:

Inclusion Criteria: Published systematic reviews/meta-analysis, cohort studies, and clinical research trials comparing risk of venous thrombosis in women using a levonorgestrel-releasing intrauterine device versus oral contraceptives.

Exclusion Criteria: Women less than 18 years of age

Summary of the Issues

Use of combined oral contraceptives increases the risk of venous thrombosis two-to-six fold.^{1,3} Both the estrogen and progestogen of combined oral contraceptives contribute to the increased thrombotic risk.¹ On top of this, smoking doubles the risk of venous thrombosis.² It has been established that women over age 35 who smoke should not use combined oral contraceptives due to the risk for cardiovascular disease.² Therefore, in this subset of patients,

other forms of contraception with other routes of administration are being evaluated to see if they have reduced risks.

The levonorgestrel-releasing intrauterine device (LNG-IUD) is a T-shaped plastic contraceptive that is inserted in the uterine cavity where it continuously releases the progestogen levonorgestrel.³ More than eight million women have used the LNG-IUD worldwide. Plasma levels of levonorgestrel during use of a LNG-IUD are lower than during the use of progestogen-only pills. Studies of progestogen-only pills suggest that there is little or no increased risk of venous thrombosis, therefore it is expected that LNG-IUD will have little thrombotic risk. The thrombin generation-based activated protein C (APC) resistance assay is a global coagulation test that enables quantification of the net prothrombotic effect of combined oral contraceptives and can also be used to predict the thrombotic risk of the LNG-IUD.¹

Summary of the Evidence

A 2009 study assessed the thrombotic risk of the LNG-IUD. In this study, the thrombotic risk was evaluated by comparing the APC resistance before and after insertion of a LNG-IUD in 56 women. High resistance to APC is associated with an increased risk of thrombosis. In contrast to combined oral contraceptives which increase APC resistance, it was observed that the use of the LNG-IUD slightly decreased the resistance to APC in these 56 women when APC resistance was re-tested 3 months later (mean baseline 2.75 vs. mean three months later 2.47; difference -0.29; 95% CI -0.04 to -0.53).¹ In women who switched from a combined oral contraceptive to the LNG-IUD, there was an even larger decrease in resistance to APC (difference -1.48; 95% CI -0.85 to -2.11). This decrease in APC resistance suggests that the LNG-IUD does not have a prothrombotic effect and suggests that it does not increase the risk of venous thrombosis. The non-randomized design is possibly a limitation of this study. In this study, researchers compared resistance to APC before and after insertion of an IUD in the same

women so the comparison groups were equal except for the studied intervention which is the IUD. However, due to the non-randomized design, the observed decrease in APC resistance after insertion of the LNG-IUD can only be attributed to the intrauterine device.¹

In 2010, analyses were done on a large case-control study on risk factors for venous thrombosis. Risk factors for venous thrombosis associated with non-oral contraceptives including injectable depot-medroxyprogesterone acetate (DMPA) and LNG-IUDs were evaluated for this specific analysis. The original study was a large population-based case-control study on risk factors for venous thrombosis where patients younger than 70 years with a first episode of deep venous thrombosis or pulmonary embolism were analyzed from the files of six anticoagulation clinics in the Netherlands. For this specific study, premenopausal women were selected, aged 18 to 50 years, who were not pregnant nor within four weeks postpartum and were not using oral contraceptives. In this study, 446 patients and 1146 controls were included. The use of injectable DMPA contraceptives were associated with a 3.6-fold increased risk of venous thrombosis compared with nonusers of hormonal contraceptives. The use of a LNG-IUD was not associated with an increased risk (odds ratio 0.3; 95% CI, 0.1 to 1.1). Further adjustment for BMI, positive family history of deep venous thrombosis, or smoking habit only marginally affected the risk estimates. It was concluded that LNG-IUD seems to be the safest option regarding the risk of venous thrombosis, however the study was limited to first thrombotic events.³

A 2012 cohort study was done to assess the risk of venous thrombosis in users of non-oral hormonal contraception. Participants included all Danish non-pregnant women aged 15-49 free of previous thrombosis or cancer who were followed from 2001 to 2010. In this study, 1,626,158 women contributed to 9,429,128 woman years of observation, during which time 3,434 first ever venous thrombosis events were confirmed. Risk of thrombosis of users of transdermal, vaginal, intrauterine, and subcutaneous hormonal contraception was compared to

users of oral contraceptives and non-users of contraception. It was concluded that compared to non-users of hormonal contraception, transdermal patches increase the risk of venous thrombosis eight times, vaginal rings increase the risk of venous thrombosis 6.5 times, but the LNG-IUD did not cause any increased risk of venous thrombosis and may even be protective (relative risk 0.6, 95% CI 0.4 to 0.8), see Table 1.⁴

| Contraception type | Relative Risk (95% CI) |
|---------------------------------------|------------------------|
| Non-use | 1.00 (reference) |
| COC with levonorgestrel and oestrogen | 3.21 (2.70 to 3.81) |
| COC with norgestimate | 3.57 (2.98 to 4.27) |
| Levonorgestrel IUD | 0.57 (0.41 to 0.81) |
| Patch | 7.90 (3.54 to 17.65) |
| Vaginal ring | 6.48 (4.69 to 8.94) |

*Adapted from original article.

(For all results above, $p < 0.05$.)

Conclusion

Based on our research of literature, we conclude that in women over 35 years of age who smoke, Mirena (levonorgestrel-releasing intrauterine device) reduces the risk of deep vein thrombosis compared to oral contraceptives. The LNG-IUD was found to decrease the resistance to APC which indicates that this device does not have a prothrombotic effect. In all studies reviewed, the LNG-IUD did not cause any increased risk of venous thrombosis. This information will indeed change the way we practice; we will advise women over age 35 who smoke to consider Mirena for contraception.

Reference List (1-2 review articles, 2 evidence articles):

1. Vliet H, Tchaikovski S, Rosendaal F. The effect of the levonorgestrel-releasing intrauterine system on the resistance to activated protein C (APC). *Thromb Haemost* 2009; 101: 691-695.
2. Veljkovic M. Contraception for women with medical disorders. *Acta Facultatis Medicinae Naissensis* 2009; 26 (4): 211-216.
3. Hylckama Vlieg A, Helmerhorst F, Rosendaal F. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. *Arterioscler Thromb Vasc Biol* 2010; 30: 2297-2300.
4. Lidegaard O, Hougaard L. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. *BMJ* 2012; 344 (2990) 1-9.