West Middlesex University Hospital

Date of Search: 05 Jan 2017
Sources Searched: Medline, Embase, DynaMed,

Are progestogens contraindicated in coagulated patients with a history of venous thromboembolism?

Summary:

Product labels of combined oral contraceptives generally state that they are contraindicated in patients with an active or prior VTE (venous thromboembolism) event. However, there is limited data on which to draw conclusions about an association with VTE and progesterone-only contraceptive use; a causal association has not been demonstrated.

A recent cohort study (Martinelli, I, et al 2016) compared the incidence of recurrent VTE and uterine bleeding in women aged <60 who received anticoagulation with rivaroxaban or enoxaparin/VKA for confirmed VTE. It concluded that neither estogen or progestin-only hormonal therapy was associated with an increased risk of VTE in women on anticoagulant therapy. It also found that abnormal uterine bleeding occurred more frequently with rivaroxaban than with enoxaparin/VKAs.

Search Results:

1. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use.

Author(s): Martinelli, Ida; Lensing, Anthonie W A; Middeldorp, Saskia; Levi, Marcel; Beyer-Westendorf, Jan; van Bellen, Bonno; Bounameaux, Henri; Brighton, Timothy A; Cohen, Alexander T; Trajanovic, Mila; Gebel, Martin; Lam, Phuong; Wells, Philip S; Prins, Martin H

Source: Blood; Mar 2016; vol. 127 (no. 11); p. 1417-1425

Publication Date: Mar 2016

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Available in full text at Blood - from Highwire Press

Abstract: Women receiving vitamin K antagonists (VKAs) require adequate contraception because of the potential for fetal complications. It is unknown whether the use of hormonal therapy, especially those containing estrogens, is associated with recurrent venous thromboembolism (VTE) during anticoagulation. Despite the absence of data, World Health Organization guidelines state that use of estrogen-containing contraceptives confers an "unacceptable health risk" during established anticoagulation for VTE. We compared the incidences of recurrent VTE and abnormal uterine bleeding with and without concomitant hormonal therapy in women aged <60 years who were receiving anticoagulation with rivaroxaban or enoxaparin/VKA for confirmed VTE. Incidence densities in percentage per year were computed for the on and off estrogen-containing or progestin-only therapy periods. Cox regression models were fitted, with hormonal therapy (on vs off) as a time-dependent variable to derive the hazard ratio (HR) for the effects on recurrent VTE and abnormal uterine bleeding. In total, 1888 women were included. VTE incidence densities on and off hormonal therapy were 3.7%/year and 4.7%/year (adjusted HR, 0.56; 95% confidence interval [CI], 0.23-1.39), respectively, and were 3.7%/year and 3.8%/year, respectively, for estrogen-containing and progestin-only therapy. The adjusted HR for all abnormal uterine bleeding (on vs off hormonal therapy) was 1.02 (95% CI, 0.66-1.57). Abnormal uterine bleeding occurred more frequently with rivaroxaban than with enoxaparin/VKA (HR, 2.13; 95% CI, 1.57-2.89). Hormonal therapy was not associated with an increased risk of recurrent VTE in women receiving therapeutic anticoagulation.

The observed increased risk of abnormal uterine bleeding with rivaroxaban needs further exploration. © 2016 by The American Society of Hematology.

2. Less menorrhagia for women with VTE.

Author(s): Schulman, Sam

Source: Blood; Mar 2016; vol. 127 (no. 11); p. 1378-1379

Publication Date: Mar 2016

Publication Type(s): Journal Article Comment

Available in full text at Blood - from Highwire Press

Abstract: In this issue of Blood, Martinelli et al provide reassuring data that women taking oral anticoagulant therapy for venous thromboembolism (VTE) may use estrogen or progestin hormonal therapy to control the menstrual bleeding without increased risk for recurrent thromboembolism.

Database: Medline

3. Hormonal therapy and the risk of recurrent venous thromboembolism in women receiving anticoagulant treatment

Author(s): Martinelli I.; Lensing A.W.; Gebel M.; Beyer-Westendorf J.; Trajanovic M.; Lam P.; Prins M.H.

Source: Journal of Thrombosis and Haemostasis; Jun 2015; vol. 13 ; p. 8

Publication Date: Jun 2015

Publication Type(s): Journal: Conference Abstract

Available in full text at Journal of Thrombosis and Haemostasis - from John Wiley and Sons

Abstract: Background: Women of childbearing potential who receive anticoagulation with coumarin derivatives require adequate contraception because these agents may cause both fetal bleeding and severe embryopathy. In women using anticoagulants, physicians are reluctant to prescribe estrogen-containing therapies because of the documented increased risk of venous thromboembolism (VTE), despite an absence of data in the literature on the risk of recurrent VTE during anticoagulation. Aims: To compare the incidence of recurrent VTE with and without concomitant hormonal therapy in women aged < 60 years randomized to rivaroxaban or enoxaparin/vitamin K antagonist (VKA) in the randomized EINSTEIN DVT and PE trials. Methods: Incidence-densities in % per year were computed for the 'on' and 'off' hormonal therapy periods. Cox regression models were fitted, with hormonal therapy (on vs. off) as a time-dependent variable to derive the hazard ratio (HR) for its effects on recurrent VTE. Results: A total of 1888 women aged < 60 years were included in this analysis, of whom 475 received hormonal therapy (306 estrogen-containing, 217 progestin-only, including 48 who used both therapies one after the other). The accumulated patient-years at risk on hormonal therapy were 187.5 years (estrogen-containing: 109.5 years; progestinonly: 78.0 years), and 811.0 years for without use. Seven recurrent VTE events occurred during hormonal therapy and 38 events occurred in the period without use. Crude incidence-densities were 3.7% per year and 4.7% per year with and without hormonal therapy. The crude incidence-densities for estrogen-containing and progestin- only therapy were 3.7% per year and 3.8% per year. The HR, stratified for age and adjusted for pre-randomization use of hormonal therapy, active cancer and assigned treatment was 0.56 (95% confidence interval 0.23-1.39). Conclusion: Use of either estrogen-containing or progestin-only therapy was not associated with an increased risk of recurrent VTE in women receiving either rivaroxaban or enoxaparin/VKA.

Database: EMBASE

4. Oral anticoagulant therapy does not modify the bleeding pattern associated with the levonorgestrel-releasing intrauterine system in women with thrombophilia and/or a history of thrombosis.

Author(s): Braga, Giordana Campos; Brito, Milena Bastos; Ferriani, Rui Alberto; Oliveira, Luciana Correa; Garcia, Andrea Aparecida; Pintão, Maria Carolina; Vieira, Carolina Sales

Source: Contraception; Jan 2014; vol. 89 (no. 1); p. 48-53

Publication Date: Jan 2014

Publication Type(s): Research Support, Non-u.s. Gov't Comparative Study Journal Article

Abstract: Progestogen-only contraceptives (POCs) are suitable for women with thrombophilia and/or a history of venous thromboembolism (VTE). Several of these women, however, use oral anticoagulant therapy (OAT), which can impair the bleeding pattern associated with POC use. We evaluated the effects of OAT use on the bleeding pattern associated with the levonorgestrel-releasing intrauterine system (LNG-IUS) in women with thrombophilia and/or a history of VTE. This prospective cohort study followed two groups of women, all of whom were thrombophilic and/or had a history of VTE: OAT users and nonusers. Bleeding patterns, blood pressure, body mass index (BMI), weight, complete blood count and waist circumference were compared between the two groups before and 6 and 12 months after LNG-IUS insertion. The patient cohort consisted of 33 women aged 18 to 45 years old, including 16 OAT users and 17 nonusers. Body weight increased by 3.9% and BMI by 3.8% in OAT users 12 months after LNG-IUS insertion. Hemoglobin and hematocrit levels increased by approximately 10% in both groups. There was no difference between the groups in bleeding patterns, with amenorrhea being the most frequent pattern in both groups (41.2% each) 12 months after LNG-IUS insertion. OAT did not increase the frequency of prolonged and/or frequent bleeding. OAT users and nonusers had similar bleeding patterns after insertion of the LNG-IUS. Hemoglobin and hematocrit levels increased in both groups. © 2013.

Database: Medline

5. Risk of recurrent venous thromboembolism among young women after a first event while exposed to combined oral contraception versus not exposed to: A cohort study

Author(s): Le Moigne E.; Delluc A.; Tromeur C.; Mottier D.; Lacut K.; Le Gal G.; Nowak E.

Source: Thrombosis Research; Jul 2013; vol. 132 (no. 1); p. 51-55

Publication Date: Jul 2013

Publication Type(s): Journal: Article

Abstract: The risk of recurrent venous thromboembolism (VTE) in young women after a first oestrogen contraception associated VTE episode is unknown. This uncertainty has an impact on the decision whether to stop anticoagulant treatment. Our objective was to assess the risk of recurrent VTE in women after a first VTE episode on oestrogen contraception. This was a prospective cohort study in which we consecutively enrolled between 1992 and 2011 all women under 50 years with a first objectively confirmed VTE. The incidence of recurrent VTE during follow-up after stopping anticoagulation was compared between women users and non-users of combined oral contraception (COC) at the time of index VTE. Of the 241 women aged 50 or younger seen for a first VTE and followed-up after stopping anticoagulation, there were 180 COC-users and 61 non-users. Median duration of follow-up off-anticoagulants was 66 months (interquartile range: 33-103). There were 14 recurrences in COC-users and 5 cases in non-users. No significant association was found between exposure to COC and the incidence of recurrent VTE after adjustment for age or after restricting the analysis to major unprovoked VTE: incidence rate of recurrence 17.9/1,000/year (95%

CI: 9.6-33.2) in women with COC as compared with 17.6/1,000/year (95% CI: 6.6-47) with an incidence ratio of 0.7 (95% CI: 0.2-2.4, p = 0.59). The risk of recurrent VTE is low in young women after a first VTE. However, this risk is not significantly lower in women after a first VTE while exposed to combined oral contraception.

Database: EMBASE

6. Progestin-only contraception and venous thromboembolism

Author(s): Blanco-Molina M.A.; Lozano M.; Cano A.; Cristobal I.; Pallardo L.P.; Lete I.

Source: Thrombosis Research; May 2012; vol. 129 (no. 5)

Publication Date: May 2012

Publication Type(s): Journal: Article

Abstract: Combined oral contraceptives (COC) are the most popular contraceptive method in developed countries. Since their introduction there have been numerous changes and modifications in its composition with the aim to improve safety and tolerability while maintaining contraceptive efficacy. Most of the changes have been conducted on the progestin component, since most of the combinations include ethinyl estradiol as oestrogen. One of the adverse effects of COC is the increased risk of venous thromboembolism (VTE) in two clinical forms of presentation: deep vein thrombosis or pulmonary embolism. This review details the changes in haemostasis induced by progestin-only contraceptives and the risk of VTE in women who utilize this type of contraception; the relationship with other risk factors such as thrombophilia; the interactions of these contraceptives with anticoagulant treatment and finally the eligibility criteria for the use of hormonal contraception in women with previous VTE or thrombophilia carriers.

Database: EMBASE

7. One-year of follow-up of levonorgestrel-releasing intrauterine system use in patients with hemostatic disorders with and without anticoagulant therapy

Author(s): Vieira C.S.; Brito M.B.; De Oliveira L.C.O.; Pintao M.C.; Ferriani R.A.

Source: Fertility and Sterility; Sep 2011; vol. 96 (no. 3)

Publication Date: Sep 2011

Publication Type(s): Journal: Conference Abstract

Abstract:OBJECTIVE: The progestogens-only contraceptives methods seem not to impair blood coagulation. However, it is not known their effects in women with thrombophilia and/or previous venous thrombosis with or without anticoagulant therapy. Thus, our objective was to compare the effects of the lev- onorgestrel-releasing intrauterine system (LNG-IUS) on clinical parameters and complete blood count in women with hemostatic disorders with and without anticoagulant therapy. DESIGN: Prospective study. MATERIALS AND METHODS: This study inclued 30 women between 18 to 40 years-old with thrombophilia and/or previous venous thrombosis. These women were divided into 2 groups: with anticoagulant therapy (ACO, n = 16) and without anticoagulant therapy (n = 14). All these women were selected in a planning family program. The variables analysed were blood pressure (BP), body mass index (BMI), complete blood count (CBC). These variables were analysed before, after 6 and 12 months of LNG-IUS insertion. The bleeding patterns in each group were also analysed. ANOVA with Tukey post-test was used for statistical analysis. RESULTS: There was no significant difference between the groups in term of age, BMI, BP and CBC. The bleeding patttern did not differ between the groups and amenorrhoea/infrequent bleeding were the most common patterns in both groups. CONCLUSION: The use of LNG-IUS has similar effects in clinical parameters

and blood count in women with hemostatic disorders with and without anticoagulant therapy in 12 months of follow-up.

Database: EMBASE

8. Menstrual problems and contraception in women of reproductive age receiving oral anticoagulation

Author(s): Huq F.Y.; Tvarkova K.; Arafa A.; Kadir R.A.

Source: Contraception; Aug 2011; vol. 84 (no. 2); p. 128-132

Publication Date: Aug 2011

Publication Type(s): Journal: Article

Abstract: Background: Oral anticoagulation is associated with increased bleeding complications. The aim of this study was to assess the changes in menstrual loss and pattern in women taking anticoagulant treatment. Study Design: Women on oral anticoagulant (OA) treatment at the Royal Free Hospital were interviewed and completed a questionnaire about their menstrual cycle before and after commencing oral anticoagulation treatment. They were then asked to complete a pictorial bleeding assessment chart (PBAC) during their next menstrual bleeding episode. Results: Fifty-three women between the ages of 20 and 50 years participated in the study. Of these, 47 women completed a PBAC. The mean duration of menstruation increased from 5 days before starting OA therapy to 7 days after the commencement of treatment. Thirty-one (66%) of the 47 women who completed the PBAC had a score that was greater than 100. The number of women who experienced flooding or clots during menstruation and intermenstrual or postcoital bleeding also increased. In total, 29 (54.7%) women changed their method of contraception during OA treatment. Seventeen women who did not want to become pregnant were not using contraception, including 10 women who were on hormonal contraception prior to starting anticoagulant therapy. Conclusion: Women of reproductive age experience heavy and prolonged menstrual bleeding whilst on OA therapy. Women of reproductive age on OA therapy should be monitored for menstrual disorders to ensure that prompt and appropriate treatment is instituted. Advice about appropriate contraception should also be part of the medical care provided for these women. Barrier contraception, sterilization and progestin-only contraception are all suitable methods of contraception in this patient group.

Database: EMBASE

9. The Levonorgestrel Intrauterine System is an Effective Treatment in Women with Abnormal Uterine Bleeding and Anticoagulant Therapy

Author(s): Vilos G.A.; Tureanu V.; Garcia M.; Abu-Rafea B.

Source: Journal of Minimally Invasive Gynecology; 2009; vol. 16 (no. 4); p. 480-484

Publication Date: 2009

Publication Type(s): Journal: Article

Abstract: Objective: To evaluate the efficacy of levonorgestrel intrauterine systems (LNG-IUS) in obese women with AUB on anticoagulant therapy. Design: Prospective observational case series (Canadian Task Force Classification II-3). Setting: University affiliated teaching hospital. Patients: Premenopausal women on Warfarin therapy. Interventions: From January 2002 through January 2007, 10 women were identified from the senior author's clinical practice (G.A.V.). After clinical assessment, including Papanicolaou smear, endometrial biopsy, and pelvic sonography, the LNG-IUS was placed to treat their AUB. Measurements and Main Results: The median and range of age, parity, and body mass index were 45 years (34-49), 1 (0-4), and 38 kg/m2 (26-52), respectively. All

women were receiving warfarin therapy (4-12.5 mg/d) for previous venous thromboembolism. Some patients had additional comorbid conditions and were at high risk for traditional medical or surgical therapies. After placement of the LNG-IUS, all women reported menstrual reduction at 3 and 6 months. By 12 months, 1 woman with large fibroids expelled the LNG-IUS and was treated with transfemoral uterine artery embolization. Two women had amenorrhea, and 7 had hypomenorrhea. At 2 to 5 years, 1 woman expelled the LNG-IUS and hysterectomy indicated extensive adenomyosis in a 195-g uterus, and 1 woman had hysteroscopic endometrial ablation, 4 were menopausal, 2 had amenorrhea, and 1 had hypomenorrhea. In the 5 women with uterine fibroids measuring 4.2 to 147 cm3, the fibroids were reduced in volume by approximately 75% in 2, were no longer detectable in 1, were subsequently shown to be adenomyoma in 1, and required uterine artery embolization in 1. Conclusion: In properly assessed and selected obese, premenopausal women with AUB receiving warfarin therapy and at high risk for traditional therapies, the LNG-IUS was an effective treatment in 70% of patients. © 2009 AAGL.

Database: EMBASE

10. Effectiveness and safety of levonorgestrel releasing intrauterine system in treatment of menorrhagia secondary to oral anticoagulations and chronic liver disease

Author(s): Choudry A.; Malik A.; Choudry H.; Bangish N.; Hayat N.

Source: Rawal Medical Journal; 2009; vol. 34 (no. 2); p. 187-190

Publication Date: 2009

Publication Type(s): Journal: Article

Available in full text at Rawal Medical Journal - from Free Access Content

Abstract: Objective To determine whether the levonorgesterol releasing intra-uterine contraceptive device can safely reduce menstrual blood loss and improve quality of life in patients with bleeding disorders and those on oral anticoagulation. Methods Patients presenting with menorrhagia, without pelvic pathology and suffering from bleeding disorder or using oral anticoagulants had Mirena inserted at Military Hospital, Rawalpindi. Baseline hemoglobin and menstrual blood loss was evaluated using pictorial blood assessment chart. Follow up hemoglobin and menstrual assessments were performed at 3, 6 and 12 months. At 12 months, patient satisfaction was assessed. Results Eighteen patients with bleeding disorders (3 chronic liver disease and 6 on anticoagulation with warfarin) were included in the study. One patient was lost to follow up after 3 months. Remaining were followed for one year. Continuity rate was 91% at one year. Mirena resulted in decrease in menstrual blood loss by 60% at 3 months, 70% at 6 months and 85% at one year ($p<0.001$ for all). Seven (31%) became amenorrhic and another seven (31%) had intermenstrual spotting. Blood transfusion requirement was completely eliminated. Patient satisfaction was very high. Conclusion In patients with bleeding and coagulation disorders, Levonorgesterol releasingintrauterine system provided an efficacious and satisfactory choice in the treatment of menorrhagia and it reduced the need for blood transfusion and surgery. (Rawal Med J 2009;34: 187-190).

Database: EMBASE

11. Contraception for women who receive anticoagulant therapy for venous thrombosis

Author(s): Kaunitz A.M.

Source: Medicine Today; Dec 2009; vol. 10 (no. 12); p. 70-71

Publication Date: Dec 2009

Publication Type(s): Journal: Note

Database: EMBASE

12. Use of contraceptive methods by women with current venous thrombosis on anticoagulant therapy: a systematic review

Author(s): Culwell K.R.; Curtis K.M.

Source: Contraception; Oct 2009; vol. 80 (no. 4); p. 337-345

Publication Date: Oct 2009

Publication Type(s): Journal: Review

Abstract: Background: As nearly all women with venous thromboembolism (VTE) will be treated with anticoagulant therapy, it is important to consider how anticoagulation affects the safety of contraceptive use. Study design: We conducted a systematic review of the literature regarding use of contraceptive methods in women with current VTE on anticoagulant therapy. Due to the limited direct evidence that was identified, we expanded our search to include women on anticoagulant therapy for indications other than VTE and women with bleeding disorders. Results: Six articles met our inclusion criteria. Three observational studies found the levonorgestrel-releasing IUD (LNG-IUD) was an effective treatment for menorrhagia for women on anticoagulation therapy or with bleeding disorders. Prevention of recurrent hemorrhagic ovarian cysts was seen in women on chronic anticoagulation treated with depot-medroxyprogesterone acetate (DMPA) in one small observational study. Among women with bleeding disorders, no complications were seen in 16 women with placement of the LNG-IUD. One pharmacokinetic study found no statistically significant interaction between combined oral contraceptives and warfarin. Other than one case report, no evidence was found regarding the risk of recurrent thrombosis in women on anticoagulation therapy using a contraceptive method. Conclusion: The majority of studies in this review examined treatment effects of the LNG-IUD or DMPA on complications of anticoagulation and found overall beneficial effects of their use in these circumstances. Minimal evidence in women with inherited bleeding disorders suggests that insertion of the LNG-IUD does not pose major bleeding risks in these women with appropriate management. © 2009 Elsevier Inc.

Database: EMBASE

13. Levonorgestrel intrauterine system: bleeding disorders and anticoagulant therapy

Author(s): Kadir R.A.; Chi C.

Source: Contraception; Jun 2007; vol. 75 (no. 6)

Publication Date: Jun 2007

Publication Type(s): Journal: Review

Abstract: Hemostatic disorders in women are frequently associated with long-standing menorrhagia. This leads to significant morbidity and adversely affects quality of life. Management of these women poses a particular challenge; medical treatments may be contraindicated, and surgery carries

additional risks. The levonorgestrel intrauterine system (LNG-IUS) has been shown to be highly efficacy in reducing menstrual blood loss in women with normal coagulation. It is also a reliable and reversible contraceptive. Data on the use of this system in women with bleeding disorders or those receiving anticoagulant therapy are limited. Analysis of data from four reported studies suggests that LNG-IUS is a viable and safe option for the management of menorrhagia in these women. Whether the underlying hemostatic disorders lead to a shorter duration of action or prolonged irregular bleeding/spotting post insertion is unknown and requires large prospective studies. Proper counselling remains crucial for patients' satisfaction.

Database: EMBASE

Strategy 109881

#	Database	Search term	Results
1	Medline	(progestogen*).ti,ab	4631
2	Medline	exp PROGESTINS/	74878
3	Medline	(1 OR 2)	77261
5	Medline	exp "VENOUS THROMBOEMBOLISM"/	6741
6	Medline	("venous thromboembolism*").ti,ab	15029
7	Medline	(5 OR 6)	16570
8	Medline	(3 AND 7)	270
9	Medline	(anticoagulat*).ti,ab	34095
10	Medline	(8 AND 9)	2
11	Medline	exp ANTICOAGULANTS/	200662
12	Medline	(3 AND 7 AND 11)	15

13	EMBASE	(progestogen*).ti,ab	5898
14	EMBASE	exp GESTAGEN/	166027
15	EMBASE	(13 OR 14)	166667
16	EMBASE	exp "VENOUS THROMBOEMBOLISM"/	125599
17	EMBASE	("venous thromboembolism*").ti,ab	23435
18	EMBASE	(16 OR 17)	127949
19	EMBASE	(anticoagulat*).ti,ab	53519
20	EMBASE	exp "ANTICOAGULANT AGENT"/	593969
21	EMBASE	(19 OR 20)	608934
22	EMBASE	(15 AND 18 AND 21)	690
23	EMBASE	exp "ANTICOAGULANT THERAPY"/	43462
24	EMBASE	(15 AND 18 AND 23)	98
25	EMBASE	*"ANTICOAGULANT AGENT"/	38255
26	EMBASE	(15 AND 18 AND 25)	35
27	EMBASE	*GESTAGEN/	11388
28	EMBASE	(18 AND 21 AND 27)	53
29	EMBASE	(anticoagul*).ti	32456
30	EMBASE	(15 AND 18 AND 29)	22
31	Medline	(3 AND 11)	372
32	EMBASE	(15 AND 29)	81