Wednesday 1st February 2017

Dr Rukhsana Hussain

A Review of Venous Thromboembolism Risk with Hormonal Contraception

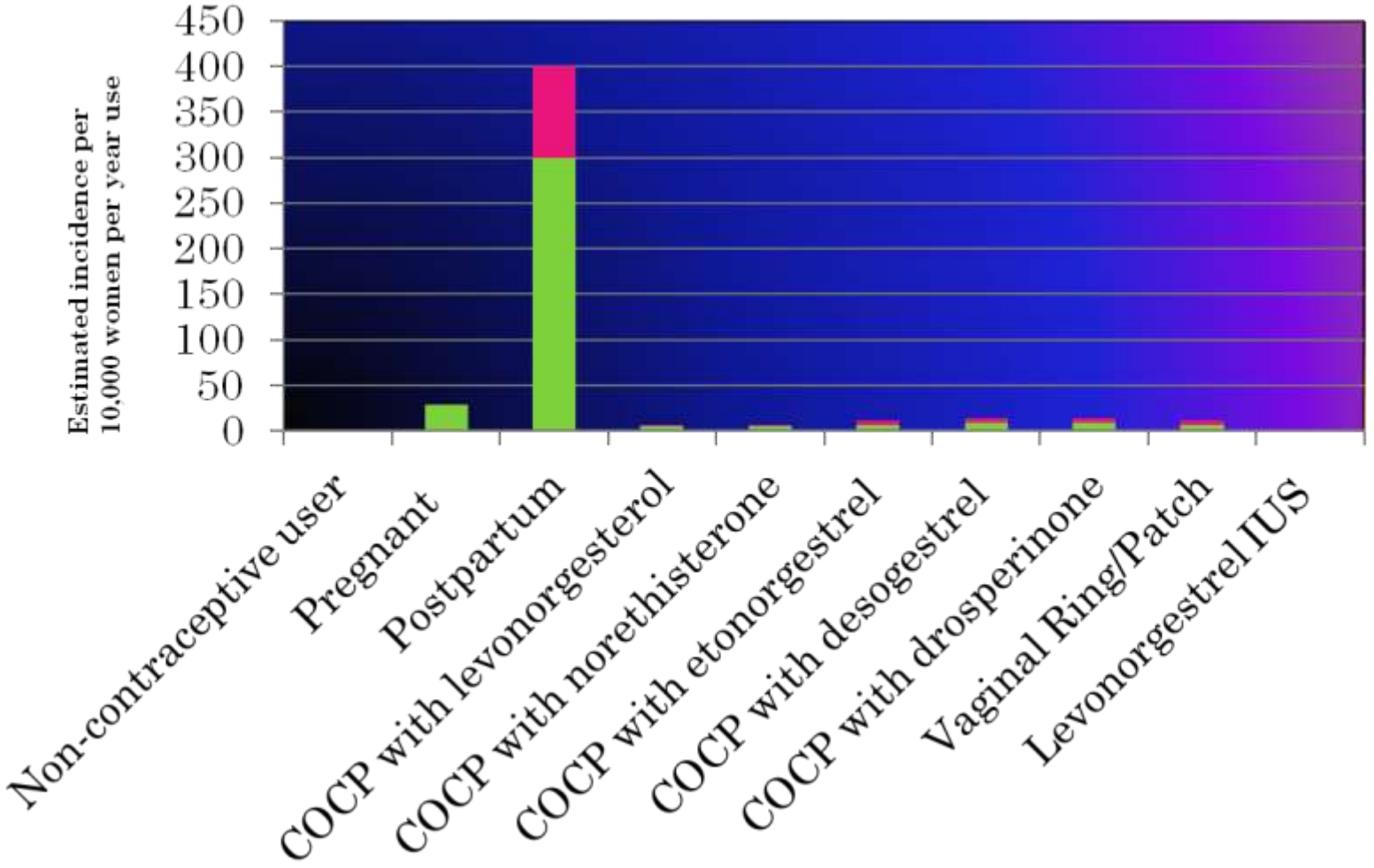
PennineGPLearning

- In 2013 the EMA (European Medicines Agency) concluded that there is good evidence to suggest that the risk of VTE associated with different combined oral contraceptives was influenced by the progestogen type.

- Different progestogens appear to modify the thrombogenic effects of oestrogen to different extents.

- **It is important to bear in mind that the absolute risk of VTE with hormonal contraception remains low though.**

VTE risk with contraceptive use



PennineGPLearning

VTE risk in numbers with estimated incidence per 10,000 women/year use

Non-contraceptive user	2
Pregnant	29
Postpartum	300-400
COCP with levonorgestrel or norgestimate or norethisterone	5-7
COCP with etonogestrel or norelgestromin	6-12
COCP with gestodene or desogestrel or drosperinone	9-14
Transdermal patch or vaginal ring	6-12
Levonorgestrel IUS	1.4

Pregnancy and the postpartum period

- Both pregnancy and the postpartum period have a much higher risk of VTE than contraceptive use.
- Pregnancy is a state of hypercoagulability (due to alteration of clotting factors), venous stasis and endothelial injury/dysfunction. [5]
- These factors alongside situations of decreased mobility and risk of endothelial injury at time of delivery combine to increase the risk of VTE in pregnancy and the postpartum period.

Risk of VTE with contraceptive use

- The highest risk of VTE is in the first 4 months of initiation of combined hormonal contraception or when restarting after a break of at least 1 month.
- Risk reduces over the next year and stabilises thereafter but is still higher than in non-users.
- Absolute risk remains **low.**
- There is little or no increased risk with the IUS, POP or progestogen implant but some evidence from small studies of a slightly increased risk with the progesterone injection.

What about Dianette (co-cyprindiol)?

- Pills containing cyproterone initially appeared to have a 4 fold higher risk than the levonorgestrel-containing COCP. This was the highest risk of VTEs with any hormonal contraceptive. Advice at the time was to limit the use of this pill to a short duration only.

- The EMA concluded after their review in 2013 that the VTE risk was only 1.5-2 times higher than levonorgestrel-containing pills and so had similar risks to COCPs containing desogestrel, gestodene or drosperinone.

- MHRA updated its advice in June 2013 stating:
  - benefits outweigh risks if women have severe acne/hirsutism.
  - it is effective as a sole contraceptive with no need for additional contraception (reports of complications in women in France were in women that had been taking Dianette and an additional COCP).
  - clinicians can continue treatment depending on the patient's need and their clinical judgement. There is no need to discontinue 3-4 months after resolution of symptoms as per previous advice.

What about norethisterone and its metabolisation to ethinylestradiol?

- Norethisterone partially metabolises to ethinylestradiol.
- Individual conversion ratios may vary but some evidence suggests that with an oral dose of 5mg norethisterone the conversion ratio is 0.4 – so 1mg norethisterone converts to 4µg ethinylestradiol. 5mg could then equate to 20µg ethinylestradiol.[1]
- For POPs in UK the maximum amount of norethisterone is 350µg and so this is not a major concern but the conversion should be taken into account when prescribing the higher dose for gynaecological conditions.

What about women with other risk factors for VTE?

- A personal history of VTE or a known thrombogenic mutation are absolute contraindications to use of combined hormonal contraception.
- In women with a family history of VTE a negative thrombophilia screen does not necessarily exclude all thrombogenic mutations and so physicians should exercise their clinical judgement when prescribing hormonal contraception.

Ukmec criteria to aid decision making regarding safety of contraception

- **UKMEC 1** – A condition for which there is no restriction to the use of the method
- **UKMEC 2** – A condition where the advantages of using the method generally outweigh the theoretical or proven risks
- **UKMEC 3** – A condition where the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable.
- **UKMEC 4** – A condition which represents an unacceptable health risk if the method is used

UKMEC summary for factors related to risk VTE (from 2016 update)

	IUS	Implant	Depo-provera	POP	CHC
Age	<20 =2 >20 = 1	after menarche = 1	<18 and >45 =2 18-45 =1	After menarche =1	<40 = 1 >40 = 2
Postpartum (not breastfeeding)					
a) 0 to <3 weeks					
- with other risk factors for VTE		1	2	1	4
-without other risk factors for VTE		1	2	1	3
b) 3 to <6 weeks					
- with other risk factors for VTE		1	2	1	3
- without other risk factors for VTE		1	1	1	2

	IUS	Implant	Depo-provera	POP	CHC
Postpartum (not breastfeeding)					
>6 weeks		1	1	1	1
Postpartum (breastfeeding)					
a) 0 to <6 weeks		1	2	1	4
b) 6 weeks to 6 months		1	1	1	2
c) > 6 months		1	1	1	1
Smoking					
a) Age <35 years	1	1	1	1	2
b) Age ≥35 years					
- <15 cigs per day	1	1	1	1	3
- ≥ 15 cigs per day	1	1	1	1	4

	IUS	Implant	Depo-provera	POP	CHC
- stopped smoking <1 yr	1	1	1	1	3
-stopped smoking ≥ 1yr	1	1	1	1	2
Obesity					
a) BMI ≥ 30-34	1	1	1	1	2
b) BMI ≥ 35	1	1	1	1	3
VTE					
a) History of VTE	2	2	2	2	4
b) Current VTE (on Rx)	2	2	2	2	4
c) Family history VTE					
-1st degree relative age -< 45 years	1	1	1	1	3
-1st degree relative age ≥ 45 years	1	1	1	1	2

	IUS	Implant	Depo-provera	POP	CHC
d) Major surgery					
- with prolonged immobilisation	2	2	2	2	4
-without prolonged immobilisation	1	1	1	1	2
e) Minor surgery without immobilisation	1	1	1	1	1
f) Immobility (unrelated to surgery eg wheelchair use/debilitating illness	1	1	1	1	3
Superficial venous problems					
a) Varicose veins	1	1	1	1	1
b) Superficial venous thrombosis	1	1	1	1	2
Known thrombogenic mutations eg factor V leiden, protein C & S deficiencies	2	2	2	2	4

Changes from UK MEC 2009 in the above summary

- For breastfeeding women re CHC (combined hormonal contraception use)
  - UKMEC 2009 6 weeks to 6 months postpartum = **3**
  - UKMEC 2016 6 weeks to 6 months postpartum = **2**

- For non-breastfeeding women re CHC use
  - UKMEC 2009 postpartum <21 days = **3**
  - UKMEC 2016 postpartum 0-3 weeks with other risk factors for VTE = **4**
    without other risk factors for VTE = **3**
  - UKMEC 2009 postpartum >21 days = **1**

    UKMEC 2016 postpartum 3-6 weeks with other risk factors VTE = **3**
    without other risk factors VTE = **2**

    UKMEC 2016 postpartum >6 weeks = **1**

Take-home messages

- Absolute risk of VTE is low with hormonal contraception in otherwise healthy women
- Risk is highest in the first 4 months after initiation of combined hormonal contraception and reduces over the next year after which it remains stable
- Dianette has a similar risk of VTE to COCPs containing desogestrel or drosperinone such as Gedarel/Marvelon and Yasmin/Lucette

- The POP, IUS and Progestogen implant have little or no increased risk of VTE
- Norethisterone partially metabolises to ethinylestradiol
- The UKMEC criteria summary is a useful resource to identify the suitability of a contraceptive method from a safety point of view

References/sources

- 1.FSRH statement Nov 2014 VTE and hormonal contraception
- 2.MHRA drug safety update re Dianette June 2013
- 3.UKMEC 2016
- 4.European Medicines agency review 2013
- 5.Medscape:Thromboembolism in pregnancy