

23. Birth control options in thrombophilia

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Q1 "Has anyone had experience with the Depot-Provera® shots? Are we allowed to take them, or not? I am asking for my daughter, who is FV Leiden positive - no coumadin, no problems."

A1: It is not known whether Depo-Provera? shots are okay to take as a contraceptive method for patients with thrombophilia, such as factor V Leiden. While progestins do not increase the risk for thrombosis in the general female population, it has not been studied whether they are also safe for thrombosis-prone individuals.

Q2 "I have 2 daughters who have FV Leiden. My oldest daughter was diagnosed after a fall which resulted in a blood clot in her entire leg, from her groin down to the toes. That was 6 years ago. My second daughter was just recently diagnosed. Is the Depot-Provera shot o.k. for them to have? One Dr. has told us yes, another said no. Everything I have read makes me believe it is not a good idea."

A2: It is not known whether Depo-Provera? shots are okay to take as a contraceptive method for patients with thrombophilia, such as factor V Leiden. While progestins do not increase the risk for thrombosis in the general female population, it has not been studied whether they are also safe for thrombosis-prone individuals.

Q3: "I found out I was hetero for FV Leiden about 2 years ago (I was 19), when I had a DVT in the leg. I was treated with coumadin for 6 months. I have been searching for a while for birth control options available to me, as obviously birth control pills or anything similar involving estrogen is out of the question. I asked my hematologist about progesterone-only contraception. He said that it should be okay, as he had never heard of any research linking progesterone with blood clots. But I am still concerned, since he couldn't tell me that he knew for sure it was reasonably safe. Just because the research isn't out there doesn't mean that an association between progesterone and clots does not exist."

A3: I think this patient is right on track. I am not aware of any research study on the use of progestin-only contraceptives in thrombosis-prone individuals. While a WHO (World Health Organization) publication in the journal Contraception [1998;57:315-324] showed that oral or injectable progestin-only contraceptives do not increase the risk of thrombosis (DVT, PE, heart attack, or stroke) in the general female population, it is not known whether they are also safe for people with history of thrombosis or with a known thrombophilia.

Q4: "My daughter, who is heterozygous FV Leiden, had been on the birth control pill for control of heavy bleeding, cramps, and irregular periods, before she was diagnosed. The hemo doc took her off. Now she would like to know, if it would be prudent for her to get back on the pill for birth control purposes, since she had no problems with the pill before, or if she could take either Depot-Provera shots or the mini pill. What are her realistic risks for either one of these options?"

A4: There is an at least 1 in 500 risk for her to develop a venous thrombosis on a combined contraceptive pill. The risk is higher if she is a smoker, and may also be higher if she is overweight or has a sedentary lifestyle. To assess an individual's realistic risk of DVT or PE, a physician also needs to know why the woman was tested for factor V Leiden (does she have a family history of blood clots? how strong is the family history?), and whether she or her family members were tested for other thrombophilic abnormalities. I can therefore not comment on the above daughter's realistic risk and whether it is prudent to go back on a combined oral contraceptive pill. It is not known whether the mini-pill (= progestin-only contraceptive) and Depo-Provera? shots are safe in people with factor V Leiden.

Q5: "If you have FV Leiden, is it o.k. to take low-dose birth control, such as Alesse® for symptoms that may be related to peri-menopause?"

A5: Alesse® is a 2nd generation combined contraceptive pill (= ethinyl estradiol 20 µg /levonorgestrel 01.mg). Even though it contains a relatively low dose of estrogen, it still increases the risk for thrombosis approximately 3-4 times compared to women who do not take oral contraceptives. In the woman who also has heterozygous factor V Leiden the risk is increased 20-30 fold. If the woman has had a venous thrombosis, Alesse® would not be advisable. If the woman never had a thrombosis, the same issues as discussed in A4 apply.

Terminology:

The words "progestin" and "progestagen" are synonyms. They are a class name for several different types of individual hormone-preparations (such as progesterone, medroxyprogesterone, norgestrel, norethindrone, etc.). The term "mini-pill" is sometimes used for progestin-only pills; the expression should not be confused with "low-dose estrogen combined contraceptives"..

Types of Contraceptive Methods

a. Non-hormonal methods

Safe contraceptive methods without an increased risk for deep vein thrombosis or pulmonary embolism are non-hormonal methods (condom, diaphragm, etc.).

b. Progestin-only contraceptives

A publication from the WHO (World Health Organization) showed that oral or injectable progestin-only contraceptives do not increase the risk of thrombosis (DVT, PE, heart attack, or stroke) in the general female population [reference 3]. However, it is not well known whether progestin-only contraceptives are also safe in people who (a) have had a previous clot or (b) have factor V Leiden or another thrombophilia. I am aware of only one published study in individuals with thrombosis or with a family history of thrombosis who took a progestin-only pill [reference 4]. This study showed that there was no increased risk of thrombosis with the progestin-only pill. However, the progestin pill evaluated in the study is not available in the U.S.

In view of the sparsity of data I think it is fair to conclude that one can not rule out a small increased risk of thrombosis with progestin-only contraceptives in people with previous blood clots or a thrombophilia. The concern about an increased risk of thrombosis with progestin-only contraceptives stems from the fact that progestins used at higher doses for purposes other than contraception (dysfunctional uterine bleeding, amenorrhea) may be associated with an increased risk of thrombosis [reference 3]. This is a scientific field that is evolving and hopefully, at some point in the future, we will have more data as to whether progestin-only contraceptives increase the risk for thrombosis in thrombosis-prone individuals or not.

Progestin-only contraceptives are:

- o Oral pills (Micronor® , Ovrette® , NOR-QD® , Camila® , Jolivette® , Errin® , Nora-BE®).
- o Depo-Provera® (= depot medroxy-progesterone)
- o Mirena IUD® - www.mirena-us.com/index.html.

The Mirena IUD releases progestins, but only low levels of progestins get into the blood stream. It may, therefore, be a particularly suitable contraceptive method in individuals with thrombosis or thrombophilia. Even though I am not aware of any systematic investigation regarding its risk of causing thrombosis, I would not expect Mirena to increase that risk.

c. Combined oral contraceptives (estrogen plus progestin)

Combined estrogen-progestin pills lead to an increased risk of DVT and PE, no matter whether one uses a low-estrogen pill or higher estrogen pill. The pills with the highest risk are the so-called 3rd generation contraceptive pills. These pills contain a certain type of progestin, called Desogestrel that leads to a higher risk of DVT and PE. I advise everybody, but particularly women with known thrombophilia, against using these contraceptive pills.

The brand names of these 3rd generation pills are:

- o Mircette®
- o Ortho-Cept®
- o Desogen®
- o Apri®
- o Cyclessa®
- o Kariva®

Yasmin® is a combined estrogen-progestin birth control pill with yet another type of progestin (drospirenone). Preliminary data [MEGA study; Rosendaal FR. Ham-Wasserman lecture; ASH, Atlanta, 12-2005] suggest that it may have a particularly high risk for thrombosis. However, no data from that study have been published yet, so that no conclusion can be made at this point.

d. Ortho Evra® patch

The Ortho Evra® patch is also a combined estrogen-progestin preparation. However, it has twice as high a risk for DVT and PE as the usual 2nd generation birth control pills. This appears to be due to the fact that the patch leads to higher blood levels of estrogens [FDA warning Feb 16,2006].

www.fda.gov/cder/drug/infopage/orthoevra/qa20060920.htm

e. Nuvaring®

The Nuvaring also contains a combined estrogen-progestin preparation. The package insert lists blood clots as a possible side effects, but whether it is a lower, the same, or a higher risk compared to usual 2nd generation birth control pills is not known at this point.

Discussion

It is not correct to categorically state, that a woman who has factor V Leiden or the prothrombin 20210 mutation should not take a combined oral contraceptive pill. The realistic (= absolute) risk for a DVT or PE of 1 in 500 for heterozygous factor V Leiden (see table) or 1 in 800 for the heterozygous prothrombin 20210 mutation may still be acceptable to many individuals. An individual decision needs to be made by every woman and her physician, based on

- whether she has had a DVT or PE or not,
- whether she smokes, is overweight, or has a sedentary lifestyle,
- whether she has a family history of DVT or PE,
- whether she is heterozygous or homozygous for the inherited abnormality,
- whether she has more than one inherited thrombophilic abnormalities,
- what her preferences are regarding progestin-only contraceptive, use of condoms, etc.
- what realistic risk of DVT or PE the woman finds acceptable and what risk she finds unacceptable.

When referring to the risk of venous blood clots associated with contraceptives, the medical literature usually states that the risk of DVT or PE is increased "x-fold", or that there is an "x-times higher risk" for venous thrombosis (= relative risk; see table column 2). For an individual person this number is not very meaningful when trying to make a decision. The patient wants to know, what her realistic risk for a clot is (= absolute risk; column 3).

Risks of developing DVT or PE:

Group of women	Relative risk (compared to women who do not take oral contraceptives)	Absolute risk: women who develop a DVT or PE per year (= incidence) (= incidence)
All women of reproductive age		1 out of 12,5000
All women on oral contraceptives	2-6 fold increased	1 out of 3,500
Women with heterozygous prothrombin 20210 mutation on oral contraceptives	16 fold increased	1 out of 800
Women with heterozygous factor V Leiden on oral contraceptives	20-30 fold increased	1 out of 500
Women with homozygous factor V Leiden on oral contraceptives	50-100 fold increased	1 out of 150

Personal comment: The advice I presently give to patients with known thrombophilia or with a history of DVT or PE who are not on warfarin is: I do not know whether progestins for contraceptive purposes increase the risk for thrombosis, but, if there is a risk, the risk is clearly less than with estrogen-containing pills. The Mirena® IUD appears to be a good option and may not increase the risk for thrombosis.

References:

1. World health Organization Collaborative Study. Cardiovascular disease and use of oral and injectable progestagen-only contraceptives and combined injectable contraceptives. *Contraception* 1998;57:315-324.
2. Rosendaal FR. Oral Contraceptives, Hormone Replacement Therapy and Thrombosis". *Thrombosis Haemostasis*,2001;86:112-123.
3. Vasilakis C et al.: Risk of idiopathic venous thromboembolism in users of progestagens alone. *Lancet* 1999;354:1610-1611.
4. Conard J et al: Progestogen-only contraception in women at high risk of venous thromboembolism. *Contraception* 2004;70:437-441.