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What are the Most Appropriate Treatments, Preventions and Family Planning Options for Patients with Factor V Leiden?

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Abstract

The management of Venous Thromboembolism in terms of treatments and prevention has been well researched for patients who have been discovered as positive for Factor V Leiden genetic clotting disorder, in either the homozygous or the heterozygous genotype. In fact, the research and development of new agents called Direct oral anticoagulants aim to treat and prevent clotting events while minimizing the risks of bleeding. Although several risk factors have been identified in relation to VTE, Factor V Leiden mutation presents a seemingly higher risk due to its unpredictable incidences of clotting events, even in patients with optimal health characteristics. Yet, we haven't transitioned to routine testing of the common population for the Factor V Leiden as a preventative measure, rather the focus has been on those at risk due to family history of VTE or if clinical decisions might depend on it, such as the proper choice of contraception for female patients. Additionally, the increased risk of thrombophilia during pregnancy raises concern for proper medical management that would benefit the mother, without harming the baby, at any point of the pregnancy.

Introduction

For many people, the thought of having a blood clot is terrifying and rightfully so because it is potentially fatal and essentially invisible. A blood clot can appear in the leg, in the lungs or even in the brain. Also called a thrombus, a clot represents an accumulation of blood in a solid state, essentially caused by coagulation processes. Although coagulation is an important and vital function of homeostasis, the resultant clot formation may obstruct blood vessels enough to limit perfusion of their field of supply. Medicine has shown that many risk factors for developing thrombi are acquired and depend on a patient's physical or medical conditions such as obesity, hypertension, atherosclerosis, or even pregnancy. However, different genetic mutations appear to be linked to increased risk of thrombosis, such as Factor V Leiden, named after the city of Leiden in the Netherlands, where it was first identified while researching links between oral contraceptives and increased cases of thrombosis (Vandenbroucke et al., 1994). Factor V Leiden is the most common genetic mutation causing increased risk of thrombophilia, or abnormal coagulation, therefore treatment options should be carefully considered for patients with clotting history, as well as preventative measures for those who have not presented with thrombi. In view of the association of blood clots with family planning measures, this review will focus on women with Factor V Leiden, considering female individuals with or without a history of thrombophilia.

Background:

Pathophysiology of Factor V Leiden

The factor V Leiden thrombophilia, also called Activated Protein C resistance, stems from a genetic mutation that affects parts of the clotting cascade, a physiological process necessary for proper regulation of coagulation (Van Cott et. al, 2016). More specifically, Activated Protein C (APC), along with a cofactor Protein S, normally inactivates some coagulation factors, hence acting as an anticoagulant system. The mutation results in a decline in that inactivation, which has the potential to increase the coagulation activity. As for all genetic mutations, they can be present as heterozygous with one abnormal copy of the gene, or homozygous, for which both copies of the gene are mutated, the latter increasing the risk for thrombophilia by 80-fold. Regarding the population distribution of the Factor V Leiden mutation, it appears to be more prevalent in Europe, followed by Africa, and less prevalent in America (Rees, Cox, 1995).

Methods

To complete this review, multiple scientific scholar databases and peer-reviewed articles mainly found on the Touro College online library were used. The Proquest, Browzine, Google scholar, and Dynamed databases were utilized with specific associations of key words in order to optimize the research and the results necessary to complete this study.

Discussion

When exploring the Factor V Leiden mutation and its relation to increased risk of venous thrombosis, it is first essential to make the distinction between individuals who have had a previous clotting event such as a deep vein thrombosis or a pulmonary embolism and those who have not. In fact, treatment options, preventative measures and family planning possibilities may be affected by a positive history of thrombophilia, regardless of the presence of any physiological risk factors, not to be dismissed, but to be utilized in conjunction with factor Factor V Leiden mutation at the time of medical management (Anderson, 2003). Those risk factors should be touched upon for reference and comparison throughout this review.

Non-genetic Risk Factors of Venous Thrombosis

The risk factors for VTE (venous thromboembolism) mainly consist of obesity, long periods of immobility, surgery, smoking, age, pregnancy and use of oral contraceptive pills, according to the NYU VTEC center and the

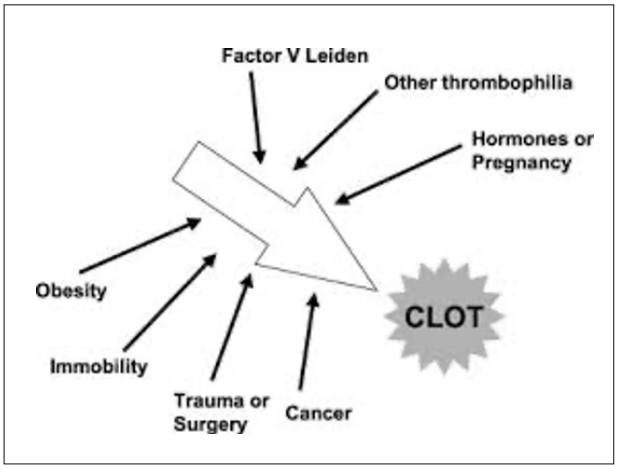

Figure 1: Most common risk factors of Venous Thromboembolism

Cornell center for blood disorders, both specializing in venous thrombosis. Although common knowledge supports their statement, others might argue about the true character of "risk factor" for some of the elements above mentioned. For instance, obesity appears as a weak link to increased VTE, based on multiple studies, therefore it should be carefully analyzed when considering treatment or even prophylaxis (Anderson, 2003). Similarly, although age seems to count as a risk factor for many diseases or medical complications, its direct connection to increased VTE is questionable, especially due to the variety of ethnicities throughout the world and their life standards, as described by an epidemiology review with respect to China presenting an impressively low rate of DVT per year (Cushman, 2007). Therefore, we should denote the importance of evaluating an association of physiological and potentially genetic risk factors when treating or preventing venous thrombosis.

Treatments and Preventions of Venous Thromboembolism

It is essential to distinguish between patients who have had a VTE event and those who haven't, as it may affect their treatment approach, even if they are positive for factor V Leiden. Additionally, this section will analyze whether treatments and preventions will be influenced by the homozygous vs heterozygous factor V Leiden status.

When discussing treatment options, we refer to patients who have actually had a DVT or a pulmonary embolism and require treatment with anticoagulant. Although the review focuses on patients with Factor V Leiden, it is important to make the comparison with patients who do not have any genetic mutation that would favor VTE, in order to better understand the rationale for treatment and prophylaxis.

Duration of Treatment

A minimum of 3-6 months of anticoagulation therapy is recommended for all patients who suffered a VTE, regardless of physiological or genetic risk factors (Kearon, Akl, 2014). However, if a VTE is unprovoked, meaning without obvious risk factor, it is highly recommended to pursue anticoagulation for at least 12 months, or perhaps indefinitely to avoid recurrence, as highlighted by multiple studies compiled in one of the articles on UPTODATE, an online medical reference, that strongly emphasized the reduction in rates of VTE recurrences in patients who had been on anticoagulation long term (Lip, Russell, 2019).

Moreover, it is debatable whether a genetic mutation causes unprovoked VTE or if it is provoked by the mutation. Even if provoked, opinions about the duration of treatment vary widely, especially if the patient's genotype is heterozygous for factor V Leiden; in fact, many providers will not treat indefinitely for a VTE provoked by a genetic factor, (Lip, Russell, 2019). More surprisingly, the actual difference in VTE incidence between both Factor V Leiden genotypes seems questionable. Indeed, when analyzing the number of actual cases and the percentage of recurrence after a first event, only a slim difference between homozygous and heterozygous percentages in VTE events (Perez Botero, Ormsby, 2016). Therefore, we can argue that the Factor V Leiden genotype shouldn't be used alone to distinguish between lengths of treatment.

On a separate note, it is essential to take into consideration the bleeding risk associated with taking anticoagulant agents, commonly named "blood thinners". As a matter of fact, all anticoagulants increase the bleeding risk to some extent and require vital risk versus benefit assessment when initiating treatment for VTE and determining duration of treatment. Bleeding associated with anticoagulation can range from a simple hematoma or easy bruising, to life threatening gastrointestinal or intracranial hemorrhage (Garcia, Crowther, 2019). Evidently, the longer a patient is on anticoagulation treatment, the higher chances he/she has of developing internal bleeding events, and those shouldn't be taken lightly, therefore must be investigated even with minimal symptoms, such as coughing up a little blood. In fact, the Mayo clinic recommends precaution when prescribing blood thinners especially to older patients (>75 years old) who present higher chances of GI bleed (Harringa, 2019). On a similar note, when treating a patient with factor V Leiden with anticoagulation on a long-term basis, one ought to carefully monitor the bleeding effect of the prescribed agent. Indeed, we can also include female patients with factor V Leiden, for which continuous anticoagulation therapy will result in heavier menstruations. Although, we previously

argued that the factor V Leiden genotype alone doesn't determine the length of treatment, those patients will need long term treatment since the factor V Leiden is a genetic component, and by definition cannot just disappear, as opposed to obesity. Therefore, if it is a constant risk factor, it will most likely represent a constant threat. The next section will present various anticoagulants that have been discovered and manufactured.

Different Anticoagulants on the Market

Table 2: Pharmacotherapy Options

Medication	Drug Class	Mechanism of Action	Daily Dosage	Renal Dosage Adjustments	Reversal Agent
Warfarin (Coumadin, Jantoven)	VKA	Inhibits formation of vitamin K dependent clotting factors II, VII, IX, X and proteins C and S	Dependent on INR	No	Yes; phytonadione (Mephyton)
Dabigatran (Pradaxa)	DOAC—direct thrombin inhibitor	Directly inhibits thrombin	150 mg twice daily	No	Yes; idarucizumab (Praxbind)
Apixaban (Eliquis)	DOAC—factor Xa inhibitor	Directly inhibits factor Xa	10 mg twice daily for 7 days, followed by 5 mg twice daily	No	None
Betrixaban (Bevyxxa)	DOAC—factor Xa inhibitor	Directly inhibits factor Xa	Single dose of 160 mg, followed by 80 mg daily for 35-42 days	CrCl >30 mL/min: no dose adjustment CrCl 15-29 mL/min: 80 mg single dose, followed by 40 mg daily CrCl <15 mL/min: use not recommended	None
Edoxaban (Savaysa)	DOAC—factor Xa inhibitor	Directly inhibits factor Xa	60 mg daily	CrCl ≥50 mL/min: no dose adjustment CrCl 15-50mL/min: 30 mg daily CrCl <15 mL/min: use not recommended	None
Rivaroxaban (Xarelto)	DOAC—factor Xa inhibitor	Directly inhibits factor Xa	Treatment: 15 mg twice daily for 21 days, followed by 20 mg daily Recurrence risk reduction: 10 mg daily	CrCl ≥30 mL/min: no dose adjustment CrCl <30 mL/min: avoid use	None

CrCl: creatinine clearance. DOAC: direct oral anticoagulants; INR: international normalized ratio; VKA: vitamin K antagonists. Source: Reference 19.

Table 1: Oral Anticoagulant comparative table

Based on the table above, multiple factors are to be considered when initiating a patient on oral therapy following an acute VTE event, especially when the patient is positive for factor V Leiden, and will most likely require long term anticoagulation therapy The drug class can be taken into account . In this case, both warfarin and the rest of the agents called Direct Oral anticoagulants (DOACs) are acceptable for treatment of VTE (Milling, Frontera, 2017). Furthermore, the daily dosage varies among all AC agents, from once a day with Warfarin or Xarelto, to twice a day with Eliquis or Pradaxa. Therefore, it raises an obvious question of medication compliance. Surely patients would be more likely to comply with their medications if only they needed to be taken once a day instead of twice a day. In that respect, Warfarin or Xarelto seem to be optimal options. However, as indicated on the table above, the daily dose of warfarin is dependent on a standardized international blood test called INR. In fact, patients on warfarin need to check their INR blood test quite often as their dose of warfarin will be adjusted based upon the results. Therefore, the frequent change of coumadin dosage undoubtedly will result in patients confused with dosage, that is without considering frequent venipunctures to test the INR. In addition, warfarin is a vitamin K antagonist, which means all foods high in vitamin K will counteract the effect of coumadin; hence, those foods should be avoided or eaten in small portions all throughout the duration of the treatment with warfarin; a factor to consider greatly since a lot of greens or even garlic can interact with warfarin (Mayo Clinic, 2018).

The next component of the table includes the creatinine clearance, representing a potential risk of certain DOAC agents such as Xarelto, on the renal function. Although it doesn't directly concern a DVT or a PE, certain patients who present with blood clots events, may also suffer from other medical conditions such as renal disease, which in this case can render the choice of AC more challenging.

The last component of the table indicates the possibility to reverse AC agents due to overuse or excess bleeding for example as a result of hypovolemic shock or major trauma. Warfarin's reversal agent is Vitamin K. Moreover, a reversal agent became approved by the FDA for both Eliquis and Xarelto this year, by the name of Andexanet Alfa (Cuker et. al., 2019).

Besides for the factors indicated on the table above, it is essential to also mention the potential risks of bleeding and consequent serious medical conditions such as GI bleed and intracranial hemorrhage. According to multiple trials, it appears that DOACs have a lower risk of intracranial hemorrhage or even GI hemorrhage than warfarin and therefore should be used as a first choice, if all contraindications have been carefully considered (Garcia, Crowther 2019).

Additionally, considerations must be made for female patients who are pregnant, because all the above-mentioned agents, whether Warfarin or DOACs are not indicated during any of the stages of pregnancy. Alternatives

will need to be used as needed for treatment of a VTE during pregnancy or even as a prophylactic agent; those will be contemplated in the family planning section.

The duration of anticoagulation treatment varies with the unprovoked versus provoked status of a VTE, in patients with either Factor V Leiden genotype, heterozygous or homozygous. A blood thinner treatment is designed to treat the current thrombosis, and even more importantly to prevent recurrence. The nature of the AC agent will depend on the availability of a reversible agent, the patient's current renal status and the level of compliance a provider attempts to achieve, apparently more in favor of DOACs due to decreased risk of internal bleeding, compared to warfarin. Recent tendency has it to get tested for genetic conditions such as Factor V Leiden, generally due to family history of clotting. Therefore, if a patient has a Factor V Leiden mutation, there may be some preventative measures to consider in certain cases, even if that individual has never experienced a VTE.

Prevention of Venous Thromboembolism for Patients with Factor V Leiden

There are several non-genetic risk factors to venous thromboembolism (VTE), such as obesity, age, recent surgery or long immobilization states. If we also consider the positive Factor V Leiden mutation genotypes, we can understand that certain patients are at serious risk for developing thrombi, whether from a physiological or genetic standpoint, or both. Moreover, patients who have had a VTE can certainly develop another one, hence the necessity for treatment, and preventative measures. Let's explore some risk factors and analyze the preventative measures that would best benefit those at risk.

First of all, we can raise the question regarding testing for genetic mutations such a factor V Leiden for patients who have had a VTE or are family members of Factor V Leiden. As a matter of fact, knowing that condition exists can be part the prevention process. It seems that newborn or infant screening for Factor V Leiden or testing of the population is not recommended, however the recommendations seem strong for female patients of child bearing age with personal or family history of VTE, as well as those under 50 years of age with a personal history of Thromboembolism (Grody, et. al, 2001). While testing family members of Factor V Leiden genotypes carriers is important in certain cases, it appears it doesn't necessarily prevent the occurrence of VTE, unless those patients are being educated on the mutation. It is especially important to educate about VTE risks and implications in different aspects of healthcare such as after a surgery, while on oral contraceptive or even during pregnancy (Segal et. al, 2009).

Regarding the prophylactic interventions using medications, patients undergoing surgery or long-term immobilization following a surgery such as a knee or hip replacement, will be offered anticoagulation prevention via a low molecular weight heparin (LMWH). The most common of those agents is called enoxaparin, with brand name "Lovenox", available as an injectable product, that can be self-administered by the patient, but requires several calculations to determine proper dosage based on weight and monitoring with a blood test called the "Anti Xa activity" that calculates its efficacy (Busti, 2015). More precisely, the LMWH acts as an inhibitor of a factor Xa, one of several proteins involved in the coagulation cascade, which results in clotting formation, either in a normal ratio or abnormal, with consequences such as VTE. .

Another commonly used agent for prophylaxis, especially following a surgery, is warfarin, previously mentioned. In fact, it may seem undesirable for a lot of patients to go through daily injections. Although the use of prophylaxis Warfarin has been associated with more than 50 % reduction of VTE post orthopedic surgery, LMWH was concluded as a superior alternative for protection against thromboembolism post-surgery (Paj, Douketis, 2019). Moreover, the use of low dose Aspirin has been contemplated as well for prevention of VTE but is most commonly used for cardiovascular prevention such as protection from strokes or myocardial infarctions.

Although the goal of anticoagulant agents is for preventing VTE, the bleeding consequences are not to be ignored. Therefore, hospital settings also offer non-pharmacological options such as an IPC device, intermittent pneumatic compression device, that improves venous circulations in upper and lower extremities to prevent edema, as well as venous thromboembolism. However, since data hasn't shown the IPC device as a complete alternative to medicated options, according to "uptodate" latest research(Paj, Douketis, 2019), it is becoming common practice to start off with IPC devices for patients with a high risk of bleeding, and then transition to a blood thinner medication agent, as presented by the AHRQ, a government agency in charge of research and quality in healthcare systems (Maynard, 2016).

Testing for Factor V Leiden is not commonly done with the general population but focuses on family members of those with the genetic mutation. In regard to prophylaxis agents for long term immobility, such as post-surgery, different agents are available and will depend on the patient's abilities to self-administer daily injections, as well as the risk of bleeding, yet it is always important to measure the levels of risk, especially for those patients with a genetic component such as factor V Leiden mutation. The

factor V Leiden genetic mutation was discovered in relation with increased risks of VTE for female patients on oral contraception. Indeed, it appears that an important amount of the research regarding Factor V Leiden thrombophilia is associated with female individuals and attend to pregnancy or contraception related matters.

Female Patients with Factor V Leiden-Family Planning

Female patients of child-bearing age who are positive for factor V Leiden need to be aware that their genotype can affect their choices when dealing with contraception and family planning.

Contraception

It is believed that oral contraceptives, especially estrogen containing agents have the potential to increase the risk of VTE; indeed, the estrogen will increase the plasma concentration of certain clotting factors and fibrinogen, all of which are favorable to clotting formation (Busti, 2015).

Although several sources have pushed for testing patients for Factor V Leiden prior to prescribing oral contraceptives, it represents a large population of female patients being tested and consequent precautions to be taken for life with constant awareness of the genotype, when there is no guarantee one of those women will ever experience a thrombosis event. Rather, a review suggests recording a comprehensive personal and familial medical history or VTE when prescribing oral contraceptives (OCP) (Rosendaal, Koster, et. al, 1995), which seems more appropriate and targeted.

It is important to understand that the association of factor V Leiden and use of oral contraceptives cause great thrombosis risk, and has been long studied and concluded as such (Choe, Suh, 2019), therefore a female patient should always mention it to her doctor before being prescribed any oral contraceptives. Luckily, several contraceptive options have become available on the market to satisfy all preferences and medical conditions, which becomes handy for those with a history of VTE or known Factor V Leiden. For example, the oral contraceptives containing only progesterone have been categorized as little to non-affecting coagulation. Therefore, these can become an ideal option for those women at higher risk of developing VTE, such as those with factor V Leiden genotypes. Similarly, Intrauterine devices (IUD) containing only progestin, such as the Mirena, are an excellent alternative to oral contraceptives for those who can't seem to comply to the daily regimen of birth control, especially when indicated to be taken at the same time every day. It is however essential to bring to light the fact that fewer studies were conducted on progesterone-only agents, therefore more data may be necessary to fully draw the conclusion of its higher grade of safety in terms of VTE prevention (Tchaikovski, Rosing, 2010). In addition, The Journal of Community Hospital Internal Medicine published an article this year warning about the progestin-only IUD, when a female patient in her early 30's with Factor V Leiden suffered a pulmonary embolism while on that intrauterine device (Jean, 2019). Therefore, although it appeared at first that only estrogen containing oral or intrauterine agents were associated with increased risk of VTE incidences, we find it questionable whether the progestin only agents are truely safe alternative for those patients at risk such as the Factor V Leiden genotypes, or even those without the genotype but with a history of clotting. Luckily for those individuals, there is now a non-hormonal intrauterine device available such as the Paragard IUD, releasing copper as a contraception method, therefore seemingly the ideal option for those of at VTE risk. In its mechanism, the copper acts as a toxic environment for sperm, which significantly reduces the chance for fertilization of the egg (Higginbotham, 2018).

Though it seems like the ideal option, it is interesting to present the reported increase of menstrual bleeding associated with the Copper Intrauterine device, as well as cramping (Galan, 2016). Furthermore, the idea of having an internal device can be disturbing for a lot of patients and has shown serious medical consequences such as ectopic pregnancies or infections, although only shown in low percentages.

To sum it up, it appears that although ample options are available on the market for contraception, the choices become limited for patients with Factor V Leiden or patients with personal or even a family history of VTE. Although intrauterine devices optimize compliance with the regimen, they aren't always the preferred options for contraception due to their potential serious consequences. Ultimately, patients at risk of developing VTE should resort to using the copper IUD, because it doesn't contain any hormones, despite its potential increase of bleeding risk, which can be even more exacerbated for those patients who already take daily anticoagulant.

Factor V Leiden plays an important role in a patient's choice for contraception, but also during pregnancy or when planning to become pregnant.

Pregnancy

Pregnancy represents a risk factor on its own for Venous Thromboembolism. During pregnancy, a patient will be considered in a hypercoagulable state, or increased tendency to coagulate, due to higher levels of fibrinogen and certain clotting factors, as well as a vascular damage or

reshaping that the increase in weight and fluid can cause (Gibson, Powrie, 2009). Following that thought process, a risk factor should be avoided, or if cannot be, should be carefully managed; in this case management of pregnancy for patients at risk of VTE.

Patients with Factor V Leiden and/or those with a history of VTE should carefully monitor their cycles as to know when to get pregnant because of the high probability those individuals will need to modify the types of AC they take. Multiple studies have examined the optimal options for prophylaxis AC in patients who are at high risk of developing VTE or those who have a history of VTE. It appears that the current recommendations suggest the use of heparin injections throughout pregnancy and up to 6 weeks after delivery, because heparin does not cross the placenta and is not transmitted via breast milk. Therefore, it is considered a relatively safe option for both the mother and baby (Gibson, Powrie, 2009). However, while Heparin is safe for pregnancy, it is important to distinguish between unfractionated heparin, which has been linked to osteoporosis and thrombocytopenia when used long term, and low molecular weight heparin (LMWH), with less incidence of the above mentioned (De Santis, et., al, 2006). An example of LMWH is Lovenox, with the generic name enoxaparin, and has demonstrated success as a prophylactic agent against VTE in several instances world-wide, one of which was reported regarding a young pregnant patient in Nigeria with factor V Leiden homozygous who was treated with LMWH during her pregnancy due to a DVT (Dogara, et, al, 2018). Since pregnancy might occur while on an anticoagulant, it is essential for those individuals to be aware of their cycles in order to start the appropriate AC agent as soon as soon they become pregnant. The use of direct oral anticoagulants (DOACs) are still contraindicated during pregnancy. In fact, it is due to the lack of data proving them safe, the few results demonstrating a high rate of miscarriage, as well as relatively significant amount of fetal abnormalities for patients on DOACs, concluded to be directly related to the DOACs, but poorly investigated (Lameijer, et, al, 2018).

Female patients who are aware of a risk factor for VTE, usually genetic such as factor V Leiden mutation, can evidently be more prepared and educated on the precautions to take regarding anticoagulation management during pregnancy. However, many patients in fact find out about their Factor V Leiden mutation during pregnancy, as they experience a DVT or pulmonary embolism, requiring emergency treatment with LMWH, or after suffering multiple spontaneous miscarriages. Interestingly, some studies have compared the rate of first trimester miscarriages in patients with known factor V Leiden and those with known regular genotype, and the incidence of early pregnancy miscarriage doesn't seem to have a close relationship with Factor V Leiden. Rather it does when comparing later term miscarriage, possibly caused by clotting within the uterine vasculature (Jivraj, et., al, 2009). Furthermore, while Factor V Leiden had been thought more risky, it doesn't appear to affect the management of pregnant patients for VTE prevention, since several studies have yet to discover significant differences in clinical pictures between homozygous and heterozygous, (Gat, et, al, 2014).

Other forms of prevention for VTE during pregnancy include compression stockings however these have received a low grade of compliance among those women due to discomfort. Moreover, it usually can improve blood circulation in lower extremities but are limited to lower extremities.

As with all patients, pregnant patients with factor V Leiden should in addition keep a healthy lifestyle, combining a balanced diet and regular exercise, to keep proper perfusion, for theirs and their babies' sake.

Conclusion

The high incidences of VTE has stimulated much research to find optimal forms of treatment and preventative agents in the forms of Anticoagulants, whether oral or injectable, for patients at higher risk of developing Venous thromboembolism, such as those individuals with the Factor V Leiden genetic mutation. Although the newer DOACs have become more popular due to decreased necessity for close monitoring, decreased bleeding risk, and statistical efficiency in the prevention of thrombosis, it appears they still cause issues for pregnant patients, and require more extensive research to prove their safety. Fortunately, low molecular weight heparin injections have been used for management of pregnant patients since they don't cross the placenta, and they have been utilized often as a post-surgery prophylaxis on a short-term basis. Regarding the management of patients who wish to utilize contraception measures, careful attention is to be applied due to the elevated clinical relationship between the use of estrogen and episodes of VTE, but unfortunately most of the contraceptive options do not seem adequate for those high-risk female individuals, therefore requiring further research and development. Although Factor V Leiden appears to be the most popular genotype associated with VTE, multiple other genetic mutations have close relationships with increased risk of thrombosis. Since the pregnancy represents a high risk factor on its own, perhaps the thought of prenatal

testing with a thrombophilia panel doesn't seem inadequate, although the question remains about a reasonable response to the screenings in terms of prophylaxis, that would be beneficial to patients' physical health without being detrimental to their mental health, once aware that an important genetic mutation is present, especially at sensitive times such as during pregnancy.

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