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Treatment of venous thromboembolism during pregnancy

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Abstract

Background: Acute VTE occurs with an incidence of 1–2/1,000 during pregnancy and is associated with an acute mortality of 1–2%. However, data on VTE treatment during pregnancy are sparse: Even though 50 cases occur daily in the EU and US, a recent review identified only 174 cases in the literature.

Acute treatment: Standard treatment is LMWH at therapeutic doses or APTT-adjusted UFH. LMWH is at least as safe and effective as UFH in non-pregnant patients. In pregnancy, LMWH is the preferred option, because it offers better bioavailability, fewer injections, superior safety regarding HIT and osteoporosis.

Long-term treatment: VKA are contraindicated because of teratogenicity and thus heparin is used for secondary prevention. Since UFH requires therapeutic doses throughout pregnancy, carrying the risk of osteoporosis, LMWH is the drug of choice. In a recent review most patients were treated initially with LMWH, predominately with twice daily injections. Recurrent VTE occurred in 1.2%, bleeding in 1.7%, with no HIT. Whether the long-term dose of LMWH can be reduced remains unresolved: Intermediate dose LMWH has been used effectively in cancer patients, who – like pregnant women – continue to have a high pro-thrombotic burden after the initial phase.

Conclusion: Even though acute VTE is not uncommon and represents a life-threatening event during pregnancy, data are sparse, and prospective trial data are needed to answer open questions concerning treatment modalities. Nevertheless, it is evident that LMWH is the preferred option for treatment of VTE during pregnancy.

Introduction

Today, venous thromboembolism (VTE) remains the leading cause of maternal mortality in the industrialised world. Every single day, more than 50 cases of acute VTE occur in Europe and the USA – however, until recently, only 174 cases were documented in the literature, mostly in small retrospective studies and case reports [1]. Therefore, the level of evidence for the management of acute VTE during pregnancy is weak, particularly in view of a potentially life-threatening disease that requires immediate and appropriate action. However, when analysing the available data, including recent prospective trials, a clear frame work for the management of pregnant women with acute VTE emerges, and only some variance and questions remain concerning details in the management, i.e. the optimal dosing after the initial treatment phase. The present review summarises the available evidence and attempts to provide guidance to the treating physician for a safe and effective management.

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Table 1
Anticoagulant agents for the management of venous thromboembolism during pregnancy (adapted from Kher et al. 2007 [2])

Drug	Mode of action	Side effects	Clinical application
Vitamin K antagonists	Interferes with the metabolism of vitamin K-dependent coagulation factors (II, VII, IX and X)	Bleeding Miscarriage (up to 40%) VKA embryopathy (4-5%)	Not recommended during pregnancy
Unfractionated heparin	Inhibits factor IIa and to a lesser degree Xa	Bleeding Osteoporosis (around 2%) Heparin induced thrombocytopenia (HIT) Allergic skin reactions	VTE-Prevention and treatment during pregnancy
LMWH	Inhibits factor Xa and to a lesser degree IIa. Reduced binding of plasma proteins compared with UFH	Low risk of bleeding ($\leqslant$2%) Low risk minor allergic skin reactions (<2%) Low risk of HIT (0–0.16%) Low risk of fetal adverse outcome (3–4%)	VTE-Prevention and treatment during pregnancy
Low-dose aspirin	Inhibits platelet cyclo-oxygenase, and platelet aggregation	Bleeding Risk of adverse fetal outcomes	Uncertain safety in early pregnancy. Prevention of late gestational complications in women with pre-eclampsia, IUGR or APLA syndrome
Fondaparinux	Selective factor Xa inhibitor	Possible minor placental transfer Low risk of bleeding	Alternative anticoagulant for patients with immune reactions to heparins
Danaparoid	Inhibits factor Xa and to a very small degree IIa.	Risk of danaparoid cross-reactivity in heparin-intolerant patients Low risk of bleeding	Alternative anticoagulant for patients who have developed HIT

VKA: vitamin-K antagonist; UFH: unfractionated heparin, IUGR: intrauterine growth restriction; APLA: antiphospholipid antibodies.

Acute VTE during pregnancy represents a complex clinical problem and all too often the attending obstetrician or physician is unsure about the optimal management. This represents a unique challenge, as not only two particularly vulnerable patients have to be treated during a particularly critical phase, but also the pharmacological treatment is challenging, because placental passage has to be considered and drugs are being used that have not been validated in randomised control trials and which are not specifically labelled for that indication. Despite those limitations, immediate action is required to prevent life-threatening complications.

Antithrombotic agents (Table 1)

Antithrombotic drugs that are available for the treatment of VTE include unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K-antagonists (VKA) and aspirin (Table 1) [2]. In addition, Fondaparinux and Danaparoid have been used during pregnancy, primarily in patients with skin or systemic allergies or immune reactions to heparins [3,4].

Vitamin-K-antagonists (VKA)

VKA may cross the placenta and have the potential for miscarriages and severe fetal problems including bleeding and teratogenicity [2]. The incidence of VKA-embryopathy (e.g. nasal hypoplasia, mental retardation, optic atrophy, microophthalmia and bone stippeling) has previously been estimated to be around 5%, with confidence intervals reaching up to 9% [5]. Therefore, VKA have been considered contraindicated during the weeks 6 and 12 of gestation. The risk may have been overestimated, as recent prospective data suggested a lower incidence of coumarin embryopathy [6]. However, the developmental toxicity of VKA may not be limited to the first 12 weeks, as CNS-abnormalities have been observed later during pregnancy [7]. Towards the end of pregnancy, VKA may cause fetal haemorrhagic complications, as the fetal liver is yet immature and fetal levels of vitamin K-dependent coagulation factors are physiologically low [5]. Thus – in conjunction with the delivery trauma severe bleeding may occur in the neonate.

Current guidelines thus recommend that VKA should be substituted with heparin in women who receive anticoagulation during pregnancy (Grade 1A [5]).

Heparins

Fifteen years ago, UFH still was the standard anticoagulant in view of the above mentioned