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RESEARCH ARTICLE

HEPARIN INDUCED THROMBOCYTOPENIA AMONG PREGNANT WOMEN IN SUDAN: UNFRACTIONATED HEPARIN VERSUS LMW HEPARIN

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ABSTRACT

While anticoagulants are useful in many circumstances, their use during pregnancy increases the risk of hemorrhage and other adverse effects, including heparin induced thrombocytopenia (HIT). This study aimed to determine the frequency of HIT among pregnant women receiving either unfractionated heparin (UFH) or low molecular weight heparin (L.W.W.H) in Sudan. The study included one hundred sixty five pregnant ladies who were received either UFH or low molecular weight heparin L.W.W.H for different indication, and have a normal platelets count (> 150 X 10^9/l) before the administration of heparin; who were admitted to Al-Dayat labour hospital, Sudan. Platelets count was performed in day 7 from heparin administration. Thrombocytopenia, with a platelets count < 100 X 10^9/l, was observed among 10.3% (17/165) of the study group, all of them belong to UFH-related group, thus have HIT (type I or type II).We highlighted a high prevalence of HIT, regardless to the HIT type among the pregnant women who were received UFH in Sudan; therefore, it is important to recommend a routine monitoring of platelet counts and prompt investigation for the HIT antibody whenever there is a suspicion of HIT among such group in Sudan.

INTRODUCTION

The use of anticoagulants and thrombolytics in pregnancy is an important consideration. Normal pregnancy is associated with a hypercoagulable state which is, at least partly, due to increased serum levels of procoagulants such as fibrinogen and factors II, VII, VIII, X, and XII. In addition, decreased protein S levels and increased resistance to activated protein C is observed in the second and third trimesters of pregnancy (Bates *et al*., 2012). Concomitantly, serum plasminogen activator inhibitor-1 (PAI-1) and placental PAI-2 increase with pregnancy, which leads to a decreased fibrinolytic state (Bates *et al.,* 2014; Chan *et al.,* 2000). Anticoagulant therapy is indicated in pregnancy for the treatment of acute venous thromboembolic events (VTE), and as thromboprophylaxis for patients with a history of thrombosis or at significant risk of thrombosis (Kupferminc *et al.,* 1999; Robertson *et al.,* 2006; Sarig *et al.,* 2002; Bates *et al.,* 2008). Unfractionated heparin (UFH), previously used as a standard anticoagulant during pregnancy, may cause significant side effects, such as osteoporosis, heparin-induced thrombocytopenia (HIT), allergy and bleeding complications (Bates *et al.,* 2008; Greer, 2006). Low-molecular weight heparin (LMWH) has replaced UFH as it is considered safer and easier to use.

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Neither UFH nor LMWH cross the placenta, and they are not secreted in breast milk (Greer & Nelson-Piercy, 2005). While anticoagulants are useful in many circumstances, their use during pregnancy increases the risk of haemorrhage and other adverse effects, including HIT which is a serious and potentially life-threatening condition (Warkentin, 2003). HIT is defined as a decrease in platelet count during or shortly following exposure to heparin (Warkentin, 2004). It may develop in two distinct forms. HIT type I is a non-immunologic response to heparin treatment, mediated by a direct interaction between heparin and circulating platelets causing platelet clumping or sequestration, and is characterized by a mild and transient thrombocytopenia. HIT type II is an immune mediated and associated with a risk of thrombosis (Ahmed *et al.,* 2007). It has been proposed that the term "HIT type I" be changed to "non-immune heparin associated thrombocytopenia" and that the term "HIT type II" be changed to "HIT" to avoid confusion between the two syndromes (Rice, 2004).Recent data show that up to 8% of heparinized patients will develop an antibody associated with HIT (Warkentin *et al.,* 1995) and that approximately 1–5% of patients on heparin will progress to develop immune-mediated HIT with thrombocytopenia (Kelton, 2002; Baglin, 1997). At least one-third of them suffering from venous and/or arterial thrombosis (Comunale and van, 2004; Gernsheimer *et al.,* 2013). While LMWH has replaced UFH, as it is considered safer, UFH is still widely been used in Sudan without an obvious monitoring policy for its side effects. This study aimed to determine the

frequency of HIT among pregnant women receiving either UFH or LMWH in Sudan.

MATERIALS AND METHODS

This prospective study included one hundred sixty five pregnant ladies who were received heparin for different indication: one hundred and fifteen pregnant ladies were received unfractionated heparin (UFH) (UFH- related group) and fifty pregnant ladies were received low molecular weight heparin (L.W.W.H) (LMWH-related group), and have normal platelets count (> 150 X 10^9/l) before the administration of heparin; who were admitted to Al-Dayat labour hospital, Sudan. Informed consent was obtained from each subject before enrollment in the study. Five ml of venous blood was collected from each subject in day 7 from heparin administration: 2.5 ml in 3.8% trisodium citrate (9:1 vol/vol), kept on ice until centrifugation at 2500g for 30 minutes at 4°C, plasma samples were immediately frozen and stored at - 80°C for subsequent coagulation analysis; and 2.5 ml in EDTA for platelets count. Laboratory analysis was performed at the Department of Haematology, Faculty of Medical Laboratory Sciences, Alneelain. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured using coagulometer (Sysmex CA 50) which rely on scattered light detection method. Platelets cell count was performed by automated cell counter (Sysmex KX-21N). Statistical analysis was performed using statistical package for social science (SPSS) software. Evaluation of patient's data was performed using the t-test. Results with p value < 0.05 were considered statistically significant.

RESULTS

The median age of pregnant ladies was 30 year, with minimum age of 18 and maximum of 41 years. Table 1 showed the results of platelet count, PT and APTT. Mean platelets counts results were as follows: 129.4 ± 25.2 X 10^9/l UFH-related group, 158.9 ± 13.3 X 10^9/l LMWH-related group and 294.0 ± 76.1 X 10^9/l for pregnant ladies before receiving heparin. 10.3% (17/165) of the study group have a platelets count< 100 X 10^9/l, all of them from UFH- related group and none of the ladies who were received LMWH has a platelets counts < 100 X 109/l. Mean platelets count was significantly lower among UFH-related group than LMWH- related group (p 0.000). Mean PT and APTT were significantly higher among pregnant ladies before receiving heparin than before receiving heparin (p 0.000 for each parameter). None of the ladies has PT or APTT shorter than the reference value.

Table 1. Results of the PT, APTT and platelets count

	UFH-related group	LMWH-related group	P value
Number	115	50	
PT mean±SD (seconds)	19.01±3.12	18.03±1.25	0.004
APTT mean±SD (seconds)	61.57±8.65	48.48±3.17	0.000
Platelets count	129.40±25.23	158.96±13.37	0.000

DISCUSSION

Heparin is widely used as a thromboprophylaxis or as a treatment in many clinical situations during gravidness. However, it can cause serious adverse effects, including heparin-induced thrombocytopenia (HIT). In this study we compare the effect of UFH versus LMWH on the platelets count. The study included 115 pregnant ladies receiving UFH and 50 pregnant ladies receiving LMWH. None of the ladies has PT or APTT shorter than the normal, this result may indicate that, none of the ladies at risk of a thrombotic tendency. Mean platelets count was significantly lower among UFH-related group than LMWH-related group. Thrombocytopenia with a platelets count < 100 X 10^9/l was observed among 10.3% (17/165) of the study group; all of them belong to UFH-related group, thus have HIT (type I or type II). Franchini M. reported that HIT type I affects up to 10% of patients receiving heparin (Franchini, 2005). None of the LMWH-related group has a platelets counts < 100 X 10^9/l, this finding suggest that, pregnant women receiving UFH at a high risk of developing HIT and with high frequency of HIT than those receiving LMWH. We couldn't determine the prevalence of the Immune-related HIT (HIT type II), which needs a confirmation of the presence of HIT- antibodies, for a financial reason. However, we highlighted a high prevalence of HIT, regardless to the HIT type, among the pregnant women who were received UFH in Sudan, therefore, it is important to recommend a routine monitoring of platelet counts and prompt investigation for the HIT antibody whenever there is a suspicion of HIT among such group in Sudan.

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Authors contributions

Sami S. Hemadi and Mahdi H.A. Abdalla conceived the idea of the study, collected and analyzed samples and data and wrote the manuscript.

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