Endogenous thrombin generation potential: an added value parameter to individualize prophylaxis treatment in pediatric haemophiliac patients?

E. Pizzuti[1], L. Rozen[2], P.Q. Lê[1, 3], A. Ferster[3], A. Demulder[2]
[1]Hôpital d'Etterbeek-Ixelles, Pediatrics, Bruxelles, Belgium, [2]CHU Brugmann, Laboratory of Hematology/ haemostasis, Bruxelles, Belgium, [3]Hôpital Universitaire Des Enfants Reine Fabiola, Université Libre de Bruxelles, Department of Hematology and Oncology, Bruxelles, Belgium

Background/ Introduction
Haemophilia is a genetic disorder caused by a deficient factor VIII (haemophilia A) or factor IX (haemophilia B). It's a rare X-linked recessive disease. The clinical features overall depend on the levels of residual factors.

Nevertheless, significant differences have been noted in patients having the same level of coagulation factors, which is therefore not reflecting the patient clinical phenotype.

Aims
Thrombin generation assay (TGA), a method of global evaluation of the coagulation process, has been used in this study to find a relationship between clinical phenotype and TGA parameters. Moreover it could be a very important tool in both the follow-up and treatment adaptation of haemophiliac patients procedures in hemophilia patients.

Methods/Materials
We analysed the computerized medical charts (starting from the diagnosis to January 2014) and some plasma samples (taken between July 2008 and January 2014) of 35 haemophiliac A and B patients. Following exclusions criteria only 18 patients were retained. 31 citrated blood samples of these 18 patients were analysed with TGA using Calibrated Automated Thrombinography ® (CAT) as described by Hemker et al (Thrombinoscope®, Maastricht, The Netherlands). We evaluated Endogenous thrombin potential (ETP) as it represents the whole quantity of thrombin generated during the all coagulation process. Individual analysis of each patient including the computation of a clinical score defined as the number of bleeding episodes/ duration of treatment was confronted to ETP.

Results
A threshold ETP value was determined below which the bleeding frequency is increased. Moreover a statistically significant relationship between ETP and clinical phenotype was revealed.

Summary/Conclusions
To conclude, a relationship between ETP and the clinical features of haemophiliac patients was demonstrated. We suggested that TGA may be of added value in the follow-up and individualized prophylactic treatment of haemophiliac patients.

Value and implications of the anti-Xa activity monitoring in pregnant women receiving prophylactic LMWH: a retrospective study

S. Paulus[1], A. Boban[2], C. Lambert[3], C. Hermans[4]
[1]Université Catholique de Louvain, Woluwe-Saint-Lambert, Belgium, [2]Zagreb University School of Medicine, Hematology, Zagreb, Croatia, [3]Université Catholique de Louvain., Hermatology, Woluwé-Saint-Lambert, Belgium, [4]Université Catholique de Louvain, Haemostasis and Thrombosis Unit, Woluwe-Saint-Lambert, Belgium

Background/ Introduction
Continuous infusion (CI) of clotting factor concentrate has facilitated surgical procedures and intensive replacement tLow molecular weight heparins (LMWH) have stable pharmacokinetics. However, physiologic changes during pregnancy can alter pharmacokinetics of LMWH and make the biodisponibility of the drug less predictable. When starting prophylactic treatment with LMWH in pregnant woman, most physicians calculate the initial LMWH dose based on the body weight and adapt the dose according to the weight gain. An alternative method is to monitor the anti-Xa activity and adjust the LMWH dose accordingly. LMWH are for the moment the only anticoagulants available for prophylaxis of thrombo-embolism in pregnant women and prevention of severe pregnancy complications.

Aims
Therefore, we conducted a study addressing the rationality of performing an anti-Xa activity monitoring regularly during pregnancy.

Methods/Materials
We retrospectively analyzed data from pregnant women undergoing prophylaxis with LMWH followed at the Hemostasis and Thrombosis Unit of the Saint-Luc University Hospital Unit. All the patients that had anti-Xa activity done at least three times were included in the study. The measurements of anti-Xa were done regularly every 6 weeks and the dose of LMWH was increased in case of anti-Xa activity lower than 0.3 U/ml. Initial LMWH dose was adjusted to the patient body weight and its thrombotic risk. The first measurement of anti-Xa was done 10 days afterwards.

Results
Out of 173 women evaluated in the study, 79% needed LMWH dose adjustment.97 patients (56%) had one dose adjustment, 35 patients (20%) two and 5 patients (3%) three. The first augmentation of LMWH dose was needed before the patient gainedbody weight in 36,5% of cases. The average increase of the LMWH dose was 49%, 100% and 116% for the one, two and three dose adjustments, respectively. Under-dosing of LMWH, defined as anti-Xa activity <0,2 U/mL, was noted in 12% of patients on the first monitoring versus 3,5% on the last monitoring.No severe side effects occurred during the treatment. Five patients (3%) had unfavorable outcome of the pregnancy.

Summary/Conclusions
This study demonstrates that regular monitoring of anti-Xaactivity can help in maintaining the prophylactic levels of LMWH throughout the pregnancy. We also showed that the drop of anti-Xa activity does not always parallel with the weight gain in pregnant women. Therefore we recommend that LMWH dose adjustment should not be made based solely on the weight gain of the patient during pregnancy.

Validation of a ready to use Clauss fibrinogen

D. Fage, I. Courtois, E. Fosse, E. Saccomando, P. Cauchie
CHU Charleroi, haematology, Charleroi, Belgium

Background/ Introduction
The STA®-Liquid fib kit is a new reagent ready to use for the quantitative determination of fibrinogen levels in plasma by Clauss method.

Aims
This evaluation includes an assay of repeatability, reproducibility, stability and a correlation with the STA®-Fibrinogen 5 kit. This one is realized on STAR-Evolution® (Stago) within the CHU de Charleroi.

Methods/Materials
Repeatability and reproducibility are evaluated on three levels, the first by 21 intra-run determinations of citrate plasma samples and the second by two determinations during 15 days of two controls and a pool high. This pool is aliquoted and frozen at -80°C.
In a purpose of comparison, the stability study is realized on both STA®-Liquid fib and STA®-Fibrinogen 5® kit. This one consists of a measure of two controls and a pool high by both kits, once a day, until appearance of a drift of the method. Our targets values and our confidence intervals are defined by the study of reproducibility. The correlation between the two kits is realized on 30 citrate plasma samples covering the entire pathophysiological range of the fibrinogen

Results
The CV (%) obtained for the 3 levels of the repeatability are lower than those reported by the firm. Concerning the reproducibility, CV (%) of the STA®-Liquid fib kit are conform to those of GEHT (Table 1). The firm claims, for the STA®-Liquid fib, an onboard stability of 10 days and a stability of 5 days for the STA®-Fibrinogen 5 kit. The results show no drift over an evaluation period of 35 days for STA®-Liquid fib kit against a clear drift after 15 days for Fibrinogen 5® kit.
The equation of the regression line (y=0,9802x + 0,0799) demonstrates a lack of proportional and constant bias throughout the pathophysiological range studied.

	Repeatability				Reproducibility		
	Sample 1	Sample 2	Sample 3		Control Low	Control N	Pool high
n	21	21	21	n	30	30	30
Mean (g/L)	2,17	3,3	5,39	Mean (g/L)	1,23	3,16	5,93
SD (g/L)	0,07	0,06	0,09	SD (g/L)	0,06	0,21	0,28
CV (%)	3,24	1,75	1,6	CV (%)	4,93	6,78	4,72
CV_{firm}* (%)	4,9	2,1	2,1	CV_{GEHT}** (%)	7,6	7,6	7,6
*CV_{firm}: indicative manufacturer's CV				**CV_{GEHT}: standards of acceptability of GEHT 2014			