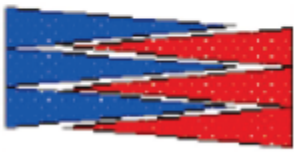
Thrombelastometrie during IVIG for the prevention of recurrent Pre-eclampsia/HELLP- Syndrome

39. Jahrestagung
der Deutschen Gesellschaft für
Klinische Mikrozirkulation und
Hämorheologie e.V.



06. und 07. November 2020, Hannover

Pregnancy and Hemostasis

- **Hypercoagulability:**

- increased Coag Fact.:	II und V	+/-	
	Fibrinogen (I)	++	(100%)
	VII	++++	(1.000 %)
	VIII, X, XII, vWF	++	(100 %)
- increased Thrombin turn-over :	TAT	++	(100 %)
- increased Fibrinogen turn-over :	**D-Dimer**, FPA	+++	(400 %)

- **Reduced Coagulation Inhibition:**

- reduced Inhibitors:	freies Protein S	--	(-50 %)
	acquired APC Resistance		40 %

- **Hypofibrinolysis (Coagulation Dissolution):**

- increased Inhibitors:	**PAI** Type I und **II**	++	(150 %)

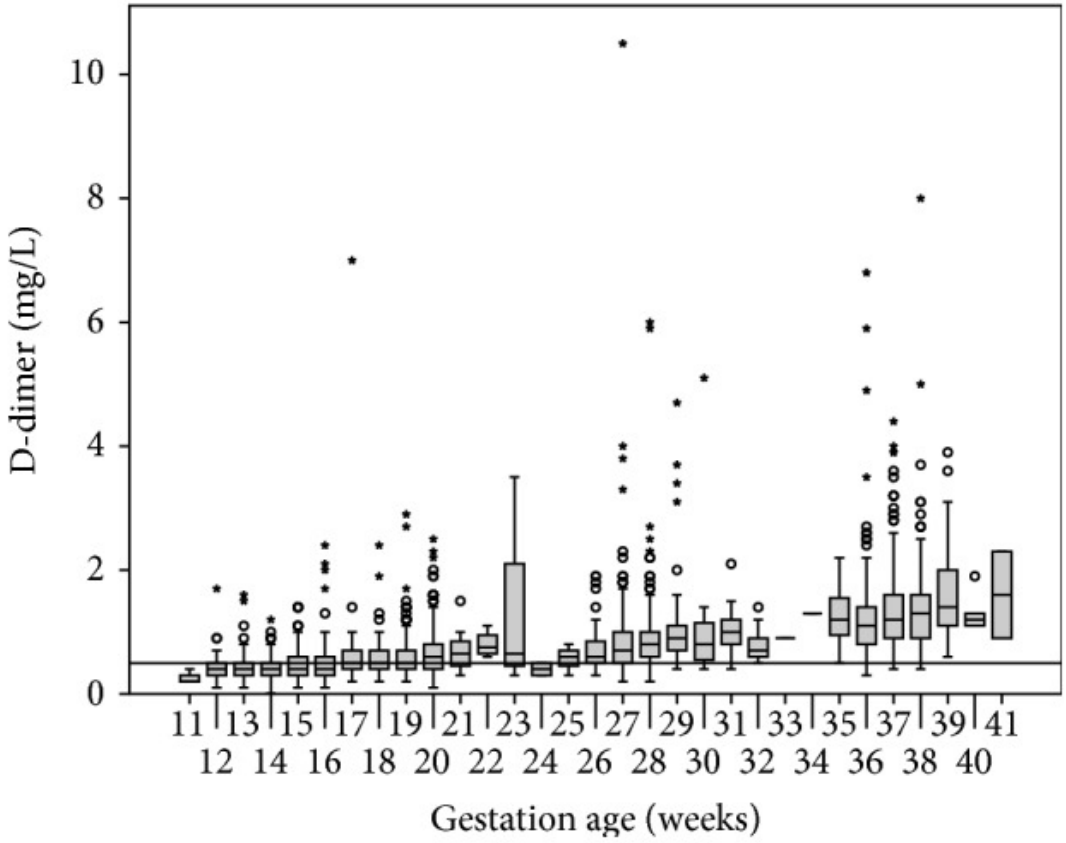
- **Thrombozytopenia:**

- 6-12 % of all pregnant women: <150.000 – 100.000 /µL

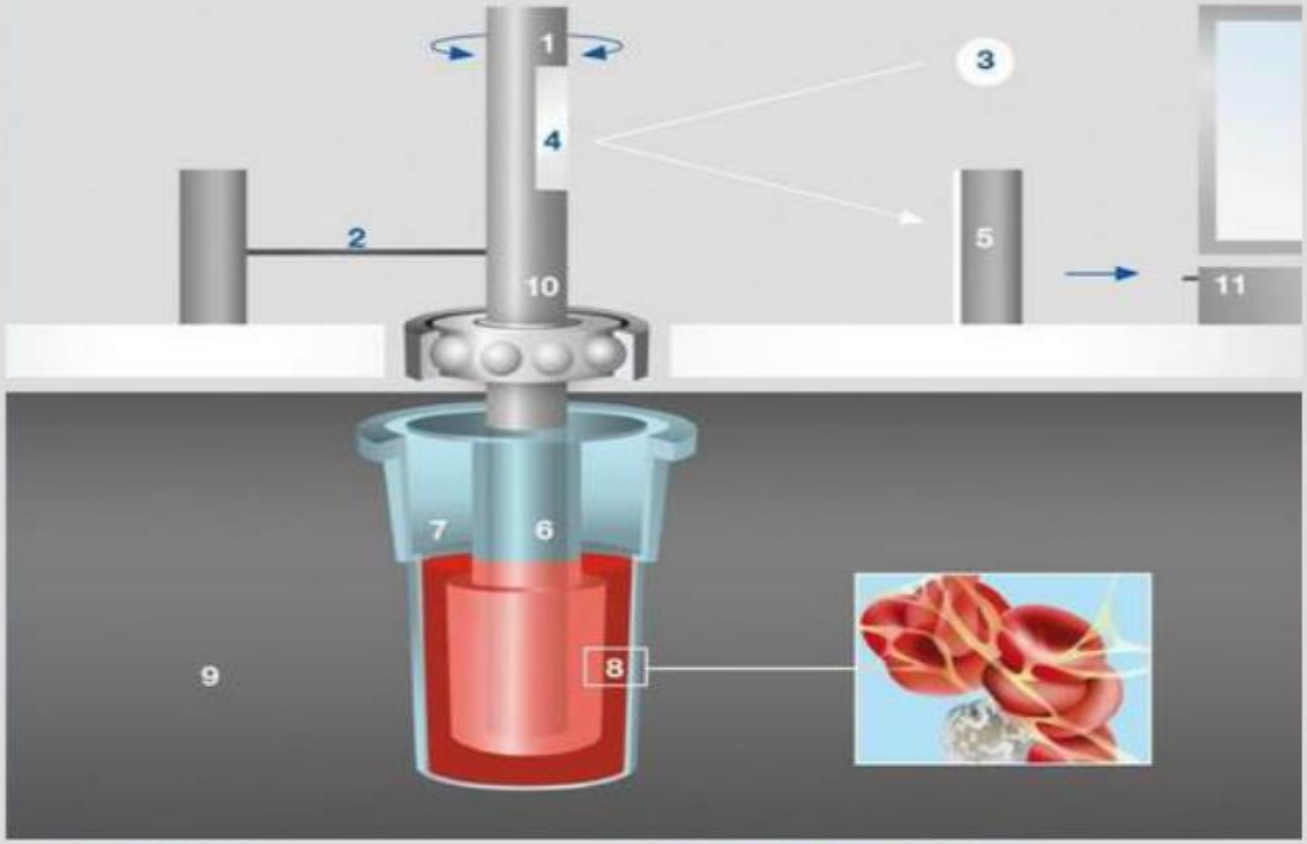
Large D-Dimer Fluctuation in Normal Pregnancy: A Longitudinal Cohort Study of 4,117 Samples from 714 Healthy Danish Women

Hedengran et al. Obstet Gynecol Int. 2016.

Box Whisker Plots D-Dimer concentration during normal pregnancy

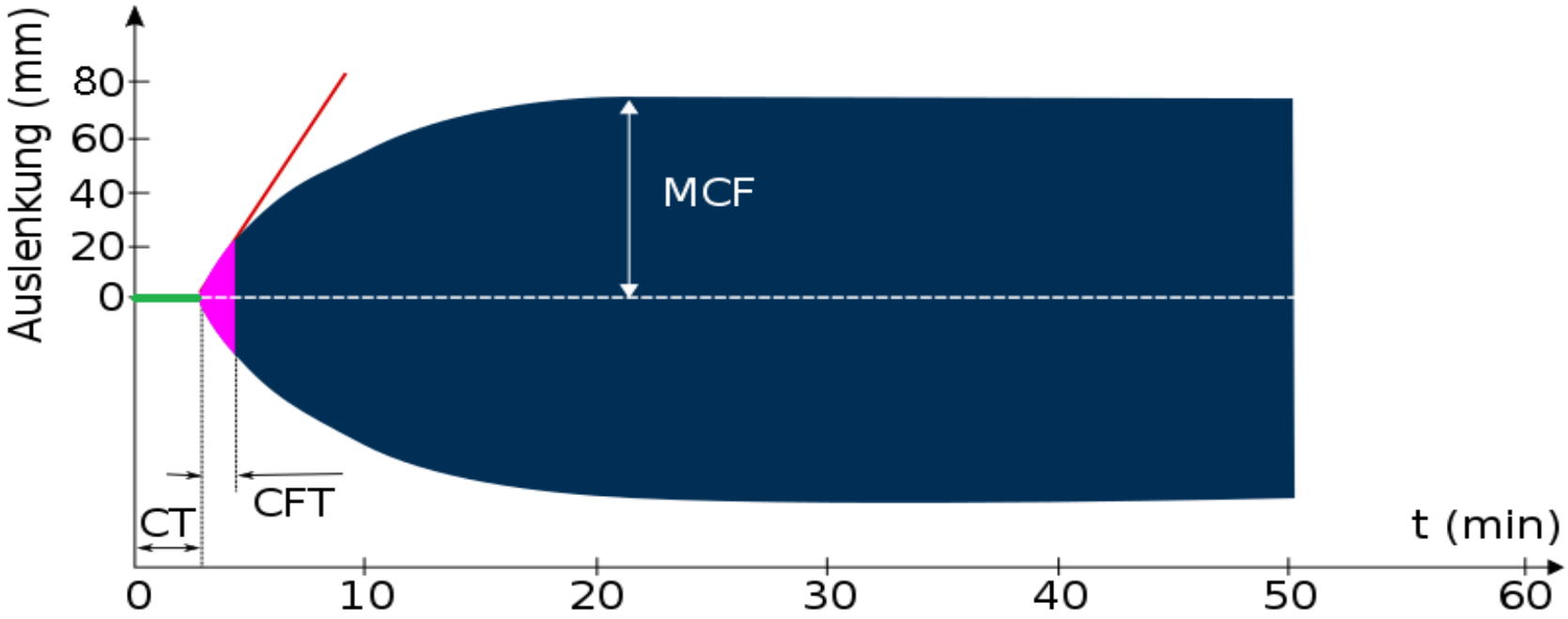


Principle of Rotem delta Thromboelastometry



1	oscillating axis	7	cuvette with blood sample
2	counterforce spring	8	fibrin strands & platelet aggregates
3	light beam from LED	9	heated cuvette holder
4	mirror	10	ball bearing
5	detector (electr. camera)	11	data processing unit
6	sensor pin		

ROTEM-Test



Clotting Time (CT): Time –point when formation starts

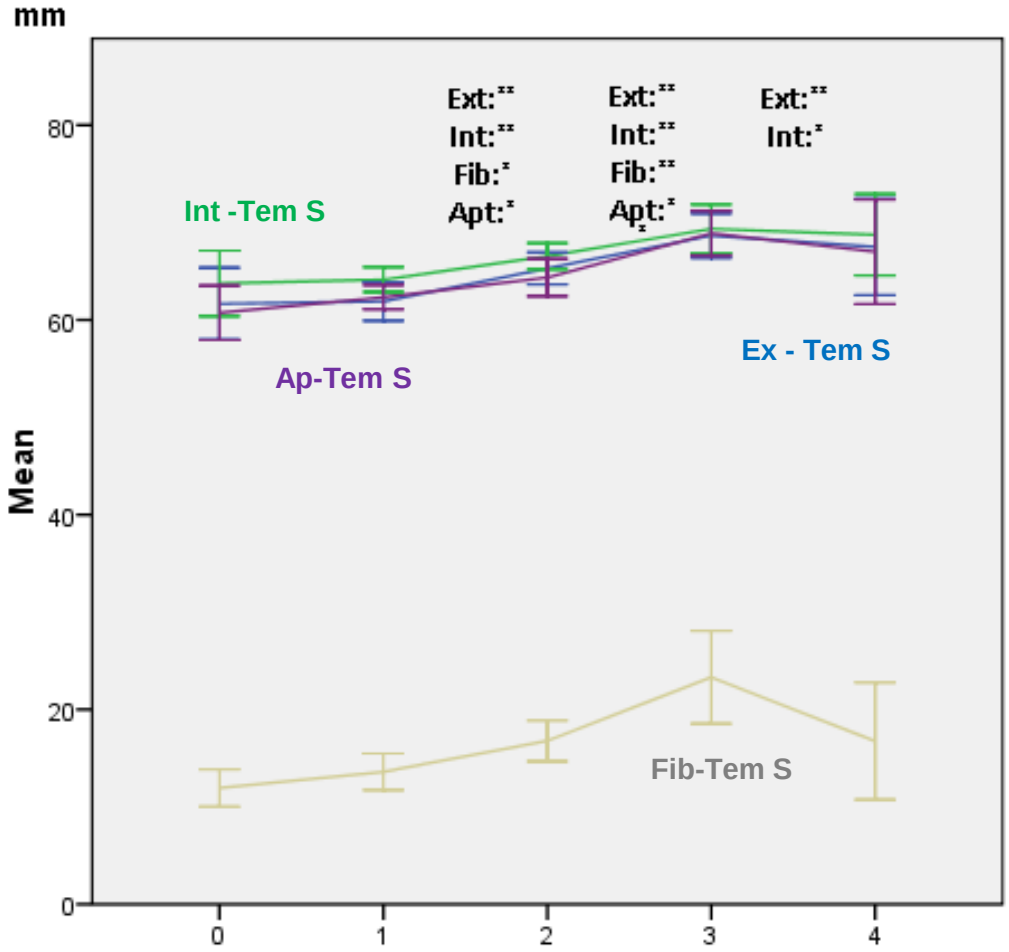
Clot Formation Time (CFT): Clotformation stabilization of 2 mm

Maximal Clot Firmness (MCF): maximal clott-firmness

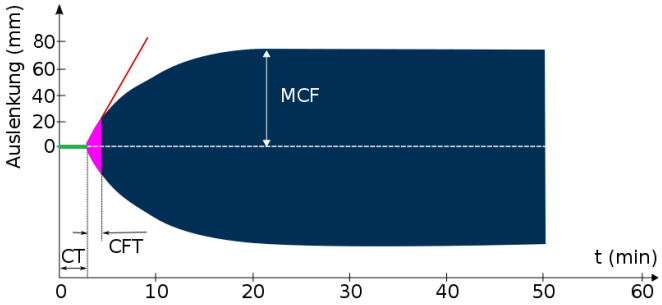
Thrombelastometric results and platelet function during pregnancy in women receiving low molecular weight heparin with a history of recurrent/late abortion-A retrospective analysis

von Tempelhoff et al.et al. Clin Hemorheol Microcirc. 2015;61:99-110.

Maximale **C**oagulation **F**irmness during normal pregnancy (**MCF**) – (**n=82**)



Mean (CI 95%)



0: before pregnancy
1: 1st Trim (< 12 GW)
2: 2nd Trim (>13 < 28 GW)
3: 3rd Trim (> 12. 27 GW)

Thrombelastometrie during IVIG for the prevention of recurrent Pre-eclampsia/HELLP- Syndrome

Thrombelastometric monitoring in

46 Patients with a history of Pre-eclampsia/HELLP- Syndrome for prevention of recurrence receiving pooled immunglobulines during subsequent pregnancy for prevention of Gestosis.

and

67 women under surveillance during normal pregnancy.

Definition of Pre-eclampsia / HELLP Syndrome (DGGG)

Pre-eclampsia (Synonyma ➔ Gestosis):

Gestational hypertension + **proteinuria** (≥ 300 mg/24h in 24-h-urine or > 30mg/mmol Protein-Creatinin-Ratio in spontaneous urine) that manifests **after GW 20**.

HELLP - Syndrome:

Trias of:

(H) hemolysis
(EL) elevated **l**iver enzymes ➔ pathological increase in hepatic enzymes
(LP) low **p**latelets ➔Thrombocytopenia (< 100.000/µl) or 50 % reduction of platelets.

Treatment during Pregnancy

when pregnancy was confirmed by positive HCG

- ASS 100 – 150 mg /d (recommandations ACOG, RCOG, DGGG….).
- IVIG (intravenous pooled immunoglobulins) 3g every 3 weeks.
- ASS and IVIG until 36_{th} gestational week.
- ASS + LMWH + IVIG in patients with APA-Syndrome.

Laboratory Monitoring in Patients and Controls

Patients:

- Before each IVIG Cycle

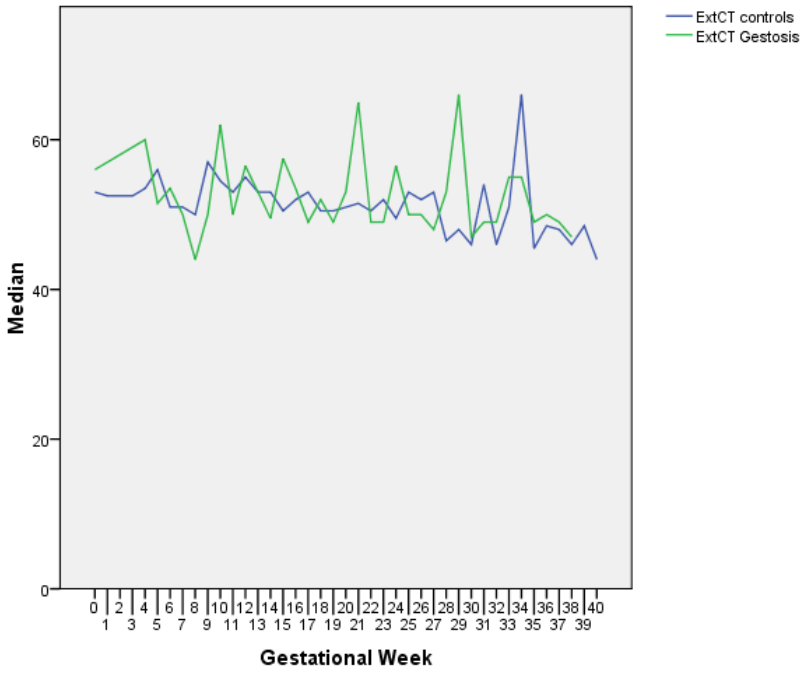
Controls:

- when visiting for regular pregnancy check-ups.

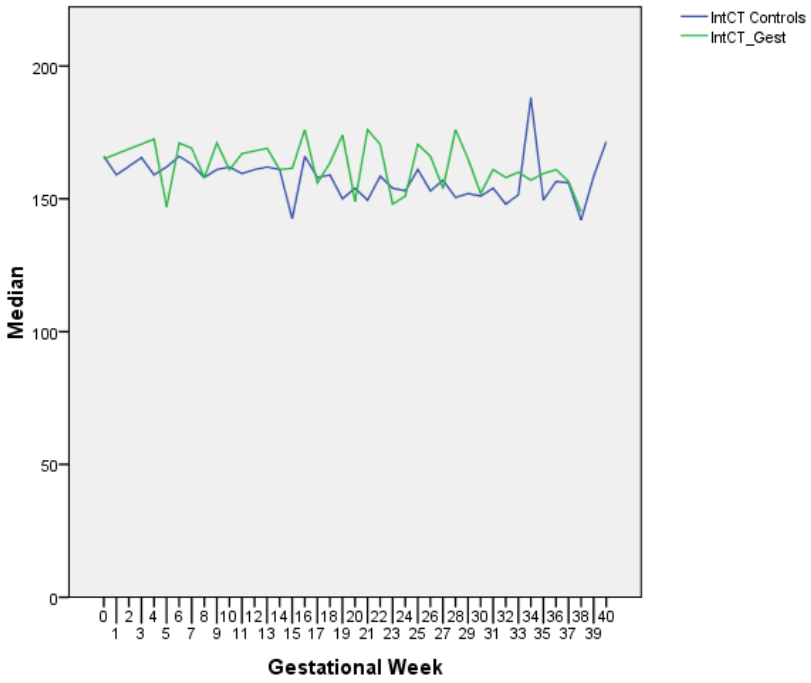
Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Clotting Time

Extrinsic Coagulation Pathway (EX-TEM)



Intrinsic Coagulation Pathway (IN-TEM)

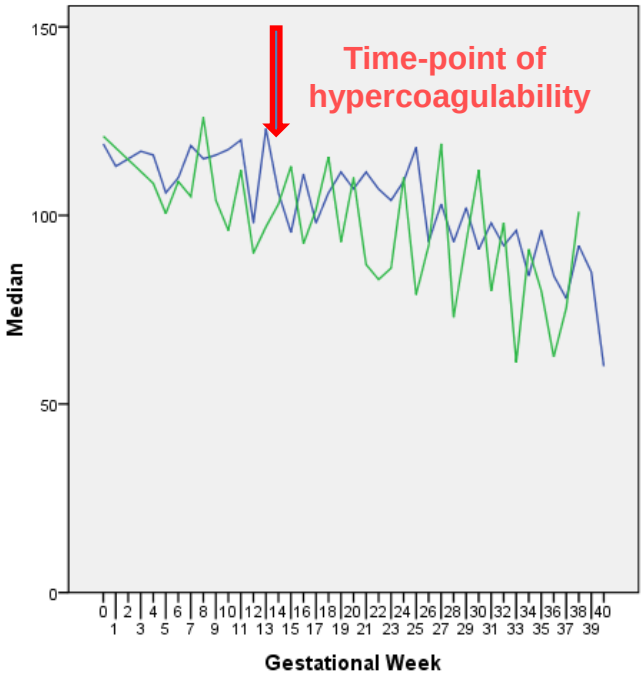


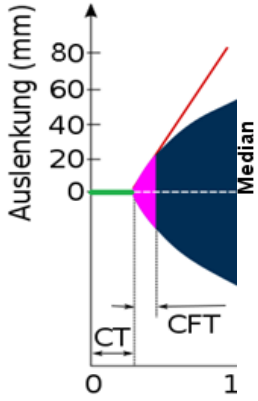
GW 0 ➔ time of clarification consultation

Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

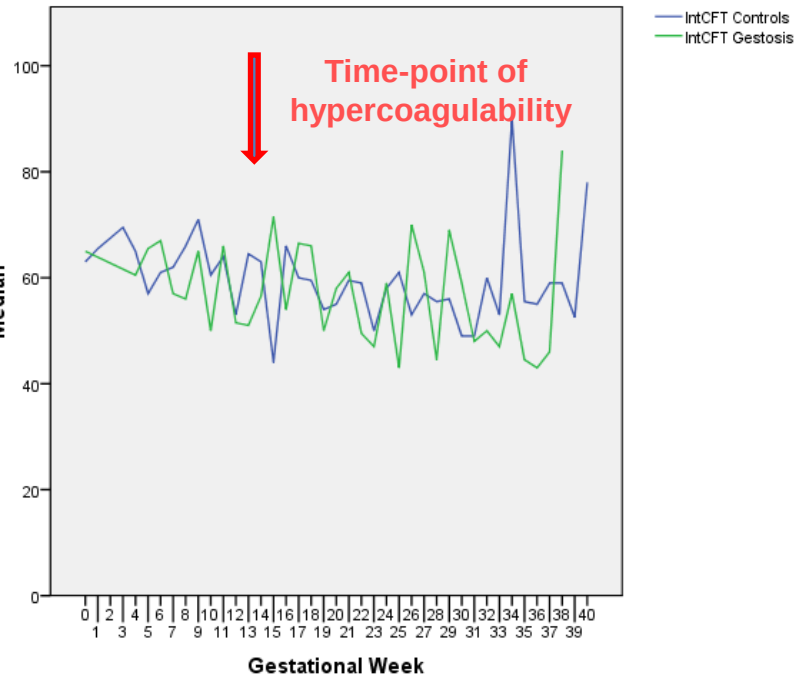
Clott Formation Time

Extrinsic Coagulation Pathway (**EX-TEM**)





Intrinsic Coagulation Pathway (**IN-TEM**)

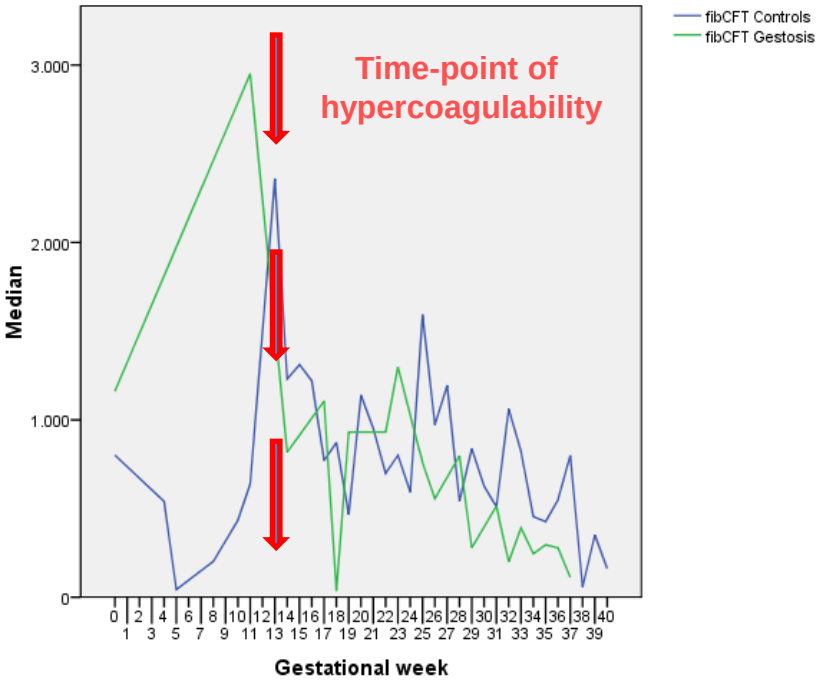


GW 0 ➔ time of clarification consultation

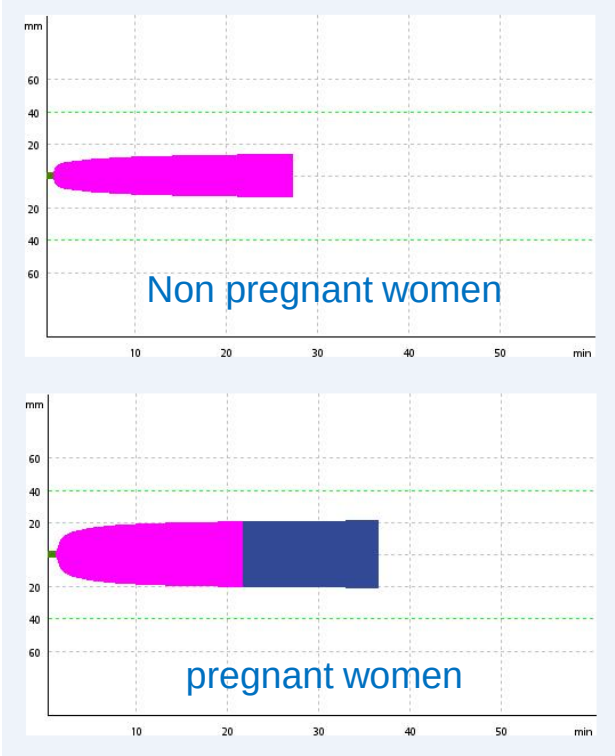
Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Clott Formation Time

Platelet blocked Coagulation Pathway (**FIB-TEM**)



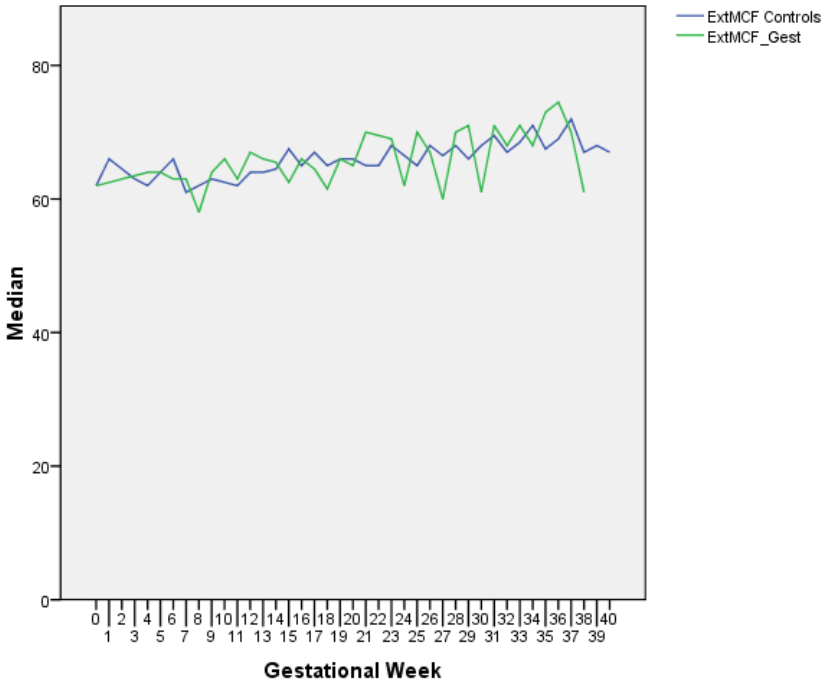
GW 0 ➔ time of clarification consultation



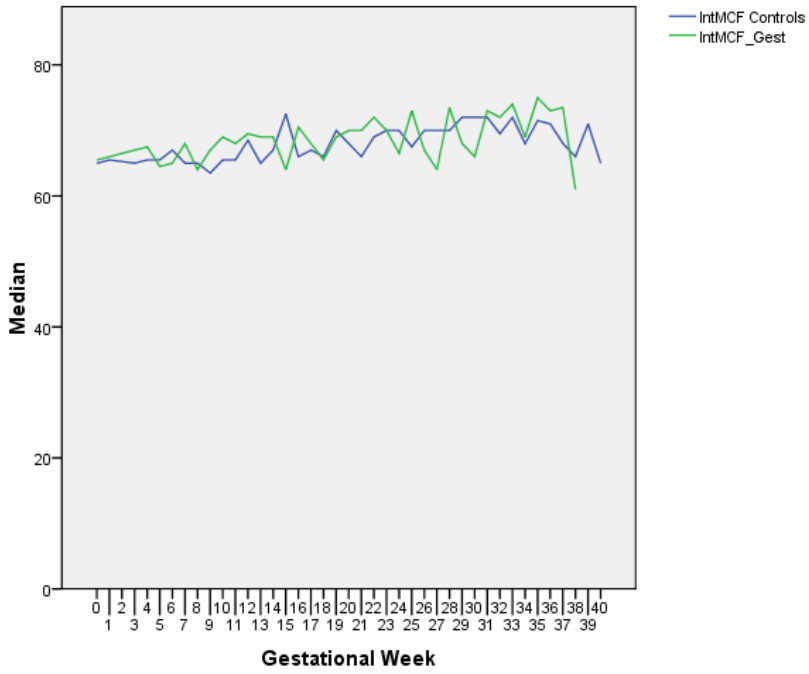
Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Maximal Clot Firmness

Extrinsic Coagulation Pathway (**EX-TEM**)



Intrinsic Coagulation Pathway (**IN-TEM**)

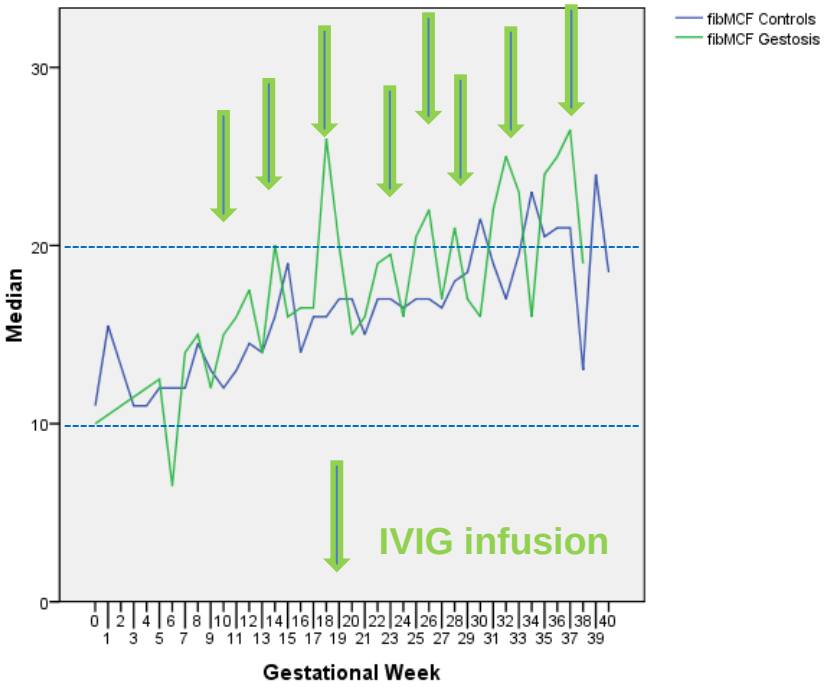


GW 0 ➔ time of clarification consultation

Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Maximal Clot Firmness

Platelet blocked Coagulation Pathway (**FIB-TEM**)

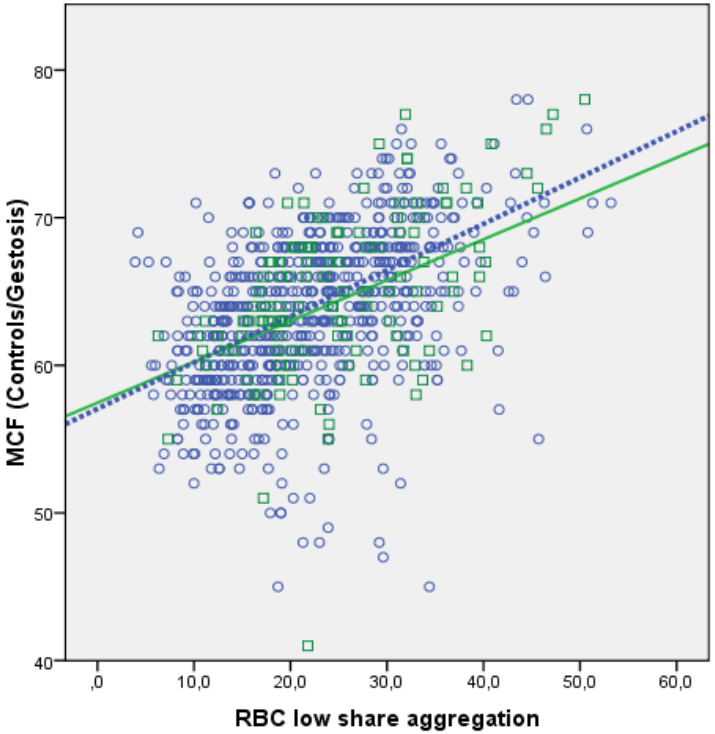


GW 0 ➔ time of clarification consultation

Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

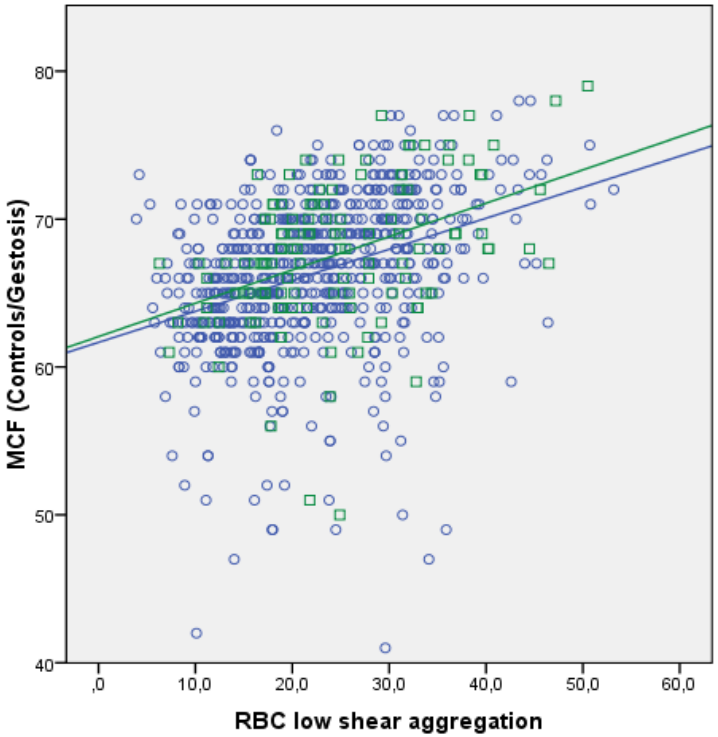
Correlation MCF and RBC low shear aggregation

Extrinsic Coagulation Pathway (**EX-TEM**)



Controls r=0,46; p<0,001
Gestosis r=0,64; p<0,001

Intrinsic Coagulation Pathway (**IN-TEM**)

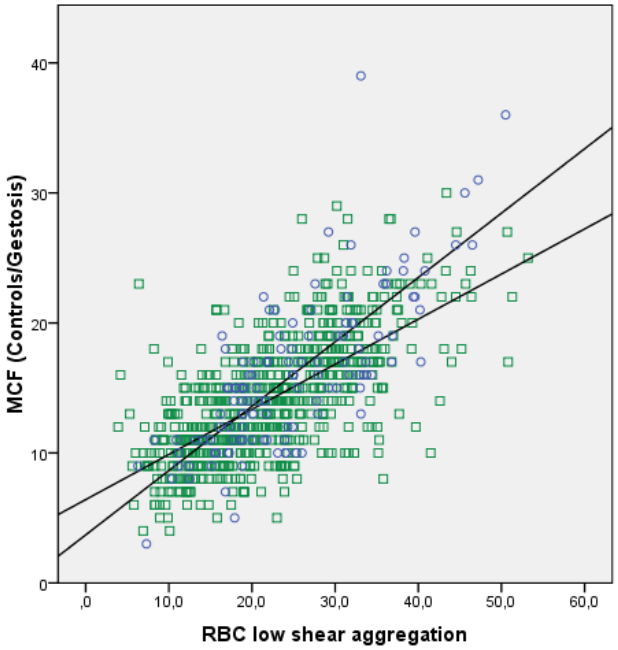


Controls r=0,34; p<0,001
Gestosis r=0,27; p=0,05

Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

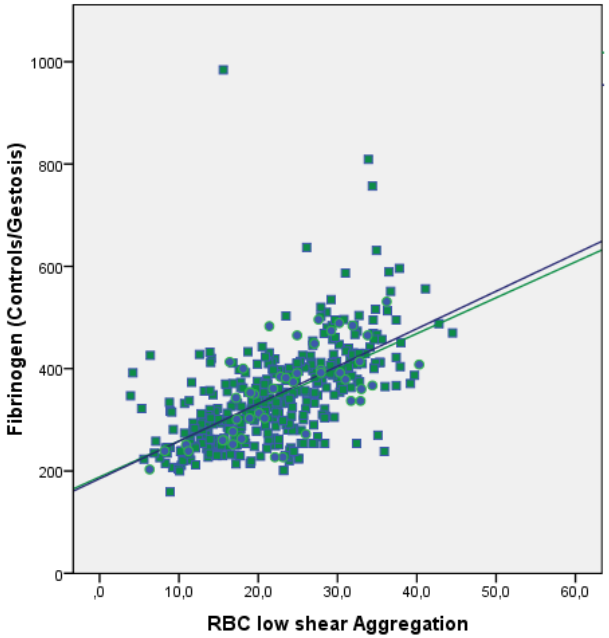
Correlation between MCF, Fibrinogen and RBC low shear aggregation

Platelet blocked Coagulation Pathway (**FIB-TEM**)



Controls r=0,51; p<0,001
Gestosis r=0,63; p<0,001

Fibrinogen concentration

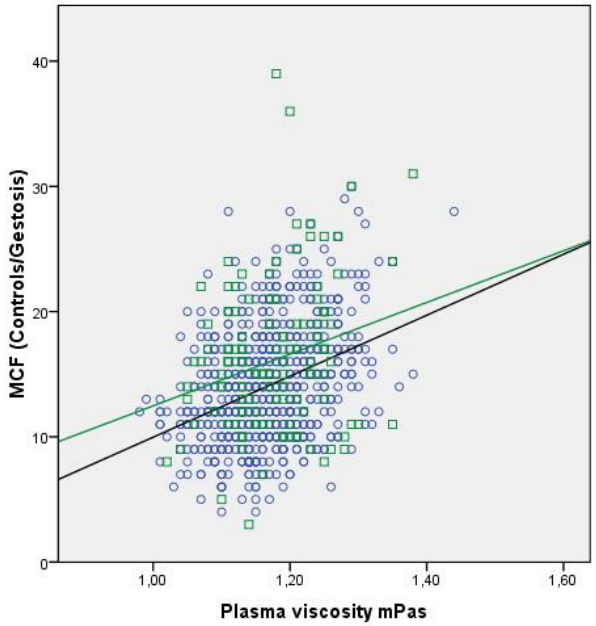


Controls r=0.46; p<0.001
Gestosis r=0.48; p<0.001

Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

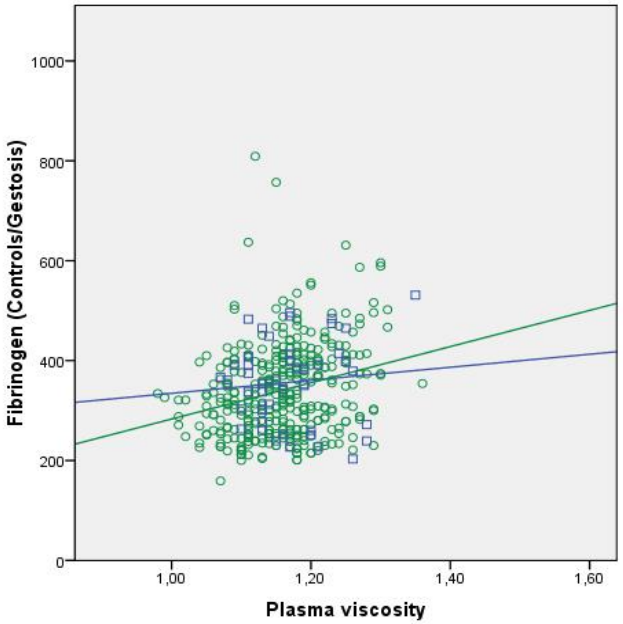
Correlation MCF and Plasma viscosity

Platelet blocked Coagulation Pathway



Controls r=0,23; p<0,001
Gestosis r=0,12; p=0,06

Correlation Fibrinogen and Plasma viscosity

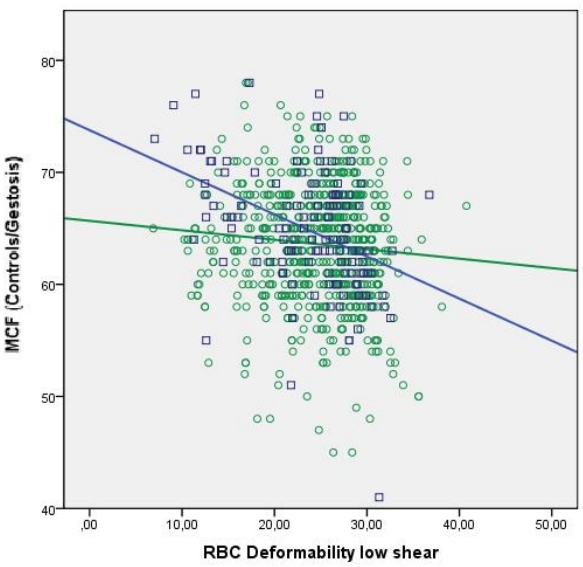


Controls r=0,17; p<0,001
Gestosis r=0,02; n.s

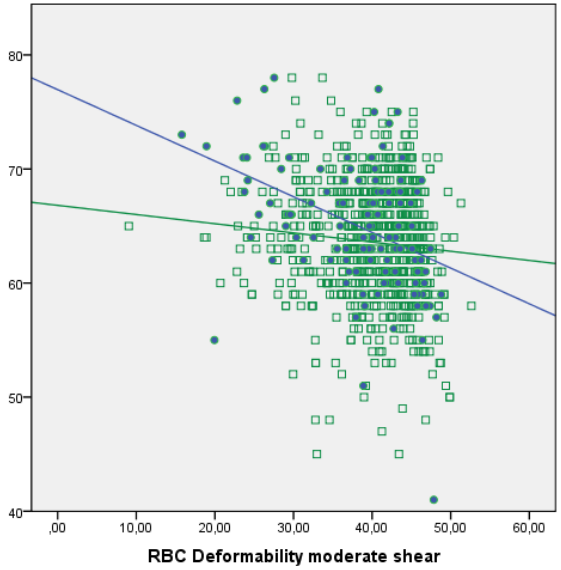
Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Correlation MCF and RBC deformability

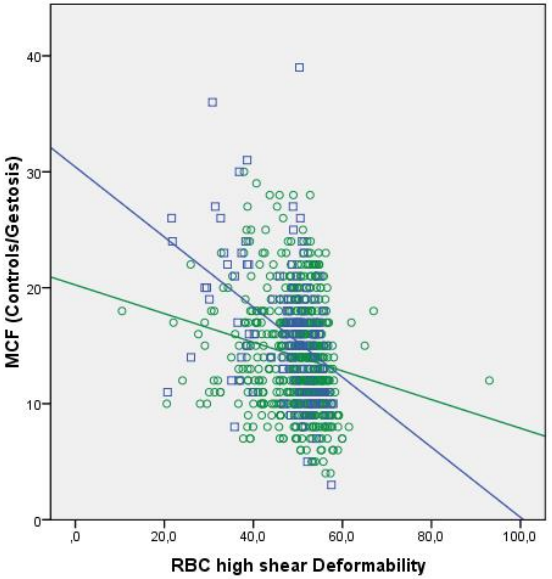
Extrinsic Coagulation Pathway (**EX-TEM**)



Controls r= -0,06; p=0,03
Gestosis r= -0,31; p<0,001



Controls r= -0,06; p=0,03
Gestosis r= -0,31; p<0,001

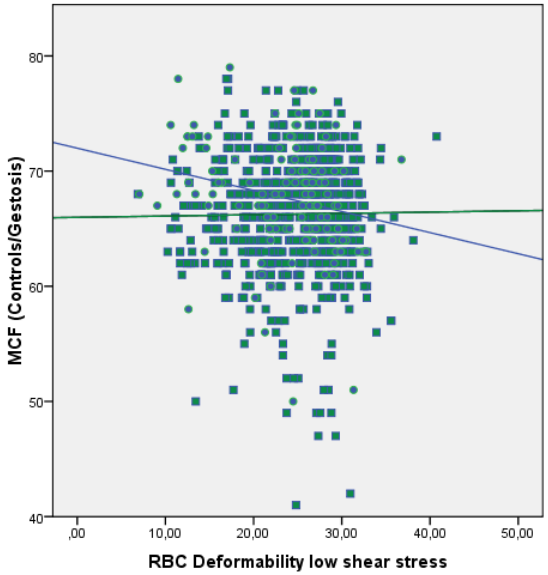


Controls r= - 0.1; p<0.001
Gestosis r= - 0,35; p<0,001

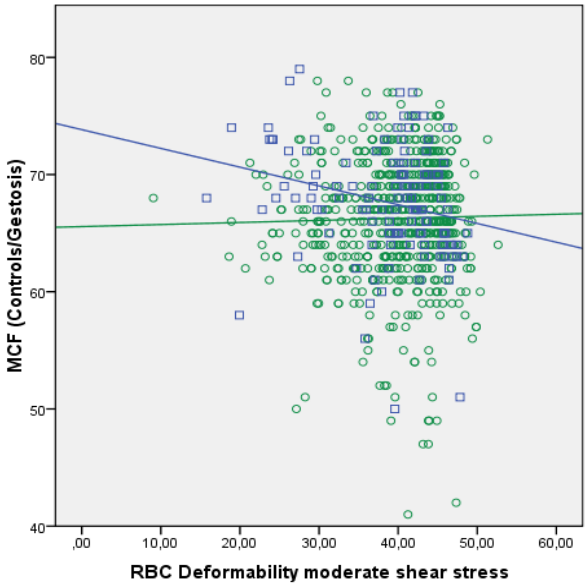
Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Correlation MCF and RBC deformability

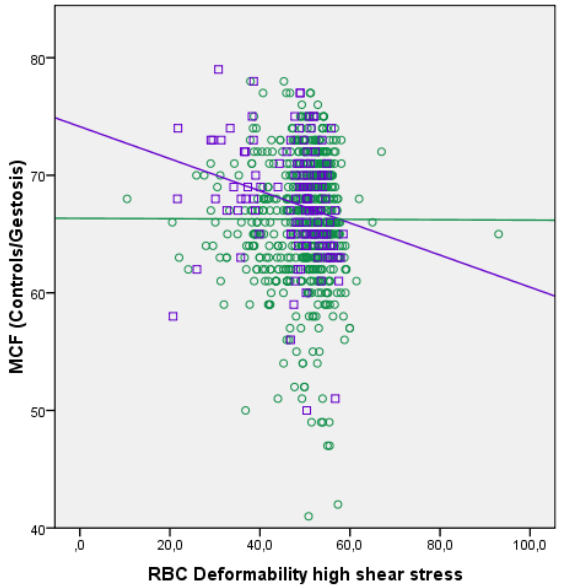
Intrinsic Coagulation Pathway (**IN-TEM**)



Controls r=0,03; n.s
Gestosis r= - 0,18; p=0,004



Controls r=0,03; n.s.
Gestosis r= - 0,19; p=0,003

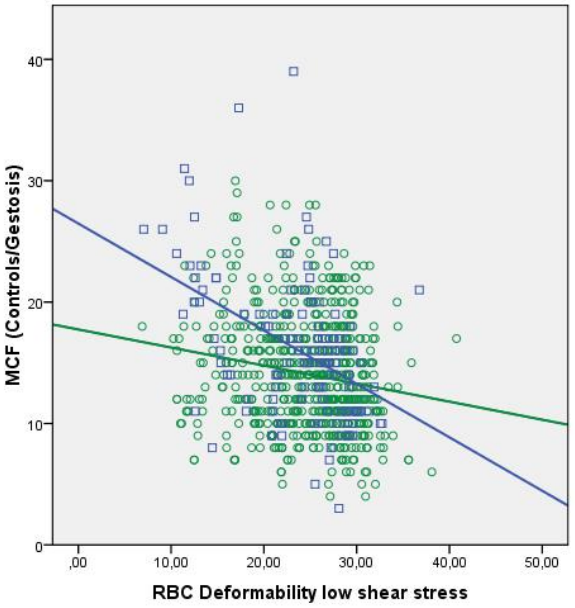


Controls r= - 0.0; n.s.
Gestosis r= - 0,22; p=0,001

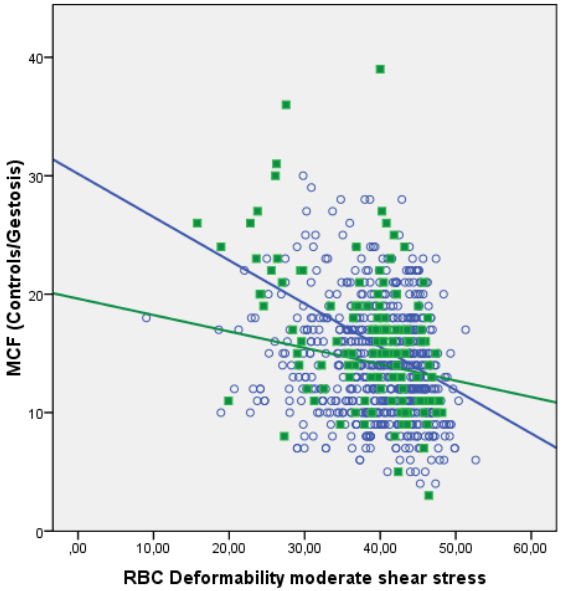
Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Correlation MCF and RBC deformability

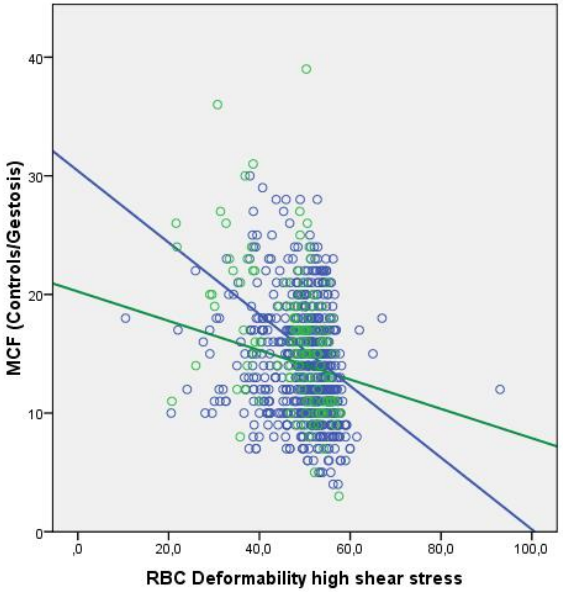
Platelet blocked Coagulation Pathway (**FIB-TEM**)



Controls r= - 0,12; p<0.001
Gestosis r=- 0,31; p<0.001



Controls r= - 0,12; p<0.001.
Gestosis r= - 0,30; p<0.001



Controls r= - 0,15; p<0.001.
Gestosis r= - 0,32; p=0,001

Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Summary

- Starting-point of significant coagulation activation is arround the 12 GW marked by CFT in platelet suppressed coagulation activation (Fib-tem) that is not reached in non pregnant women. Clot firmness after intrinsic and extrinsic coagulation activation continuously increases with the gestational age and is not different in groups.

- MCF is strongly correlated with RBC aggregation during pregnancy and ist most pronounced after platelet suppressed coagulation activation in patients receiving IVIG.
- Neither increased MCF nor Fibrinogen concentrations are accompanied by marked changes in Plasma viscosity
- MCF was significantly correlated with an increased RBC rigidity under all shear stress conditions in patients receiving IVIG and particularly pronouced after extrinsic path activation while no such association was found in normal pregnant women. .

Thrombelastometric results during IVIG for the prevention of recurrent Pre-eclampsia/HELLP Syndrome vs untreated normal pregnant women

Remark

All patients included in this evaluation gave written informed consent for the anonymous use of there data for presentation and publication.