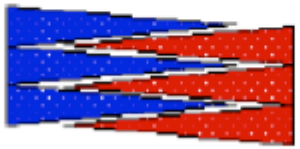
Blood Rheology during IVIG for the prevention of recurrent Pre-eclampsia/HELLP- Syndrome

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



22. und 23. November 2019, Braunschweig

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.

CAVE:

- 5-15 % no proteinuria
- upto 20 % no hypertension

Risk factor for the development of Pre-eclampsia / HELLP Syndrome (DGGG)

Autoimmune diseases	RR 7 - 9.7
Antiphospholipid antibody – Syndrome	RR ~ 9
History of pre-eclampsia	RR ~ 7
Body Mass Index > 30 kg/m^2	RR ~ 3-5
Pre existing Diabetes mellitus	RR ~ 3.5
History of Gestosis in the family	RR ~ 3
Pre existing kidney disease	RR ~ 3
primipara	RR ~ 2.5 - 3
Age > 40 Y	RR ~ 2
Essential hypertension	RR 1.55 - 3
one additional risk factor	RR 1.55
two additional risk factors	RR 3
RR diastol > 110 mm Hg (< 20 Wochen)	RR 3.2
Ethnicity (afro-american)	RR ~ 2

Risk of Recurrence after Pre-eclampsia / HELLP Syndrome (DGGG)

History of pre-eclampsia ➔ 11.5 – 27 %

History of two pre-eclamptic epsiodes ➔ **32 %**

Risk of recurrence and gestational week (GW) of previous pre-eclampsia manifestation:

≤ 28. GW ➔ **38.6 %**

29. - 32. GW ➔ 29.1 %

33. - 36. GW ➔ 21.9 %

≥ 37. GW ➔ 12.9 %

Risk of recurrence and severeness of previous pre-eclampsia:

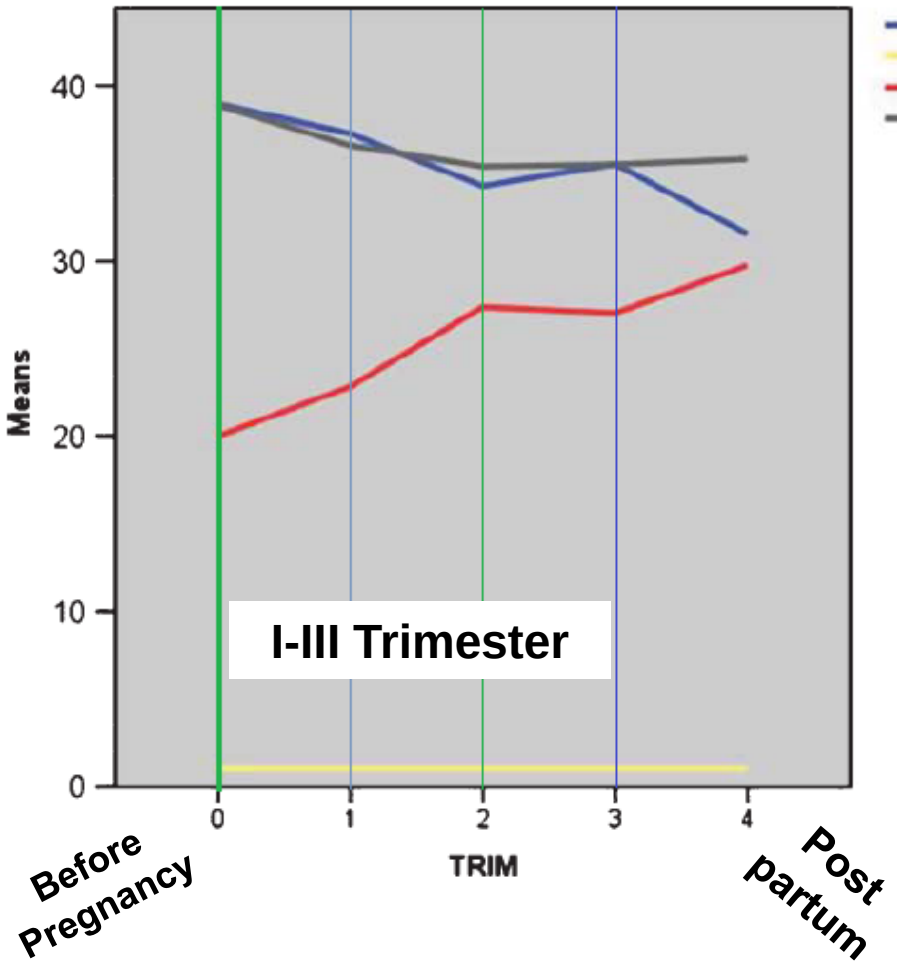
Severe pre-eclampsia < 34. GW ➔ 25 %

HELLP-Syndrome < 28. GW ➔ **55 %**

Bloodrheology during normal pregnancy

Tsikouras P, Wehrfritz O, Rath W, v.Tempelhoff G-F. Clin. Hemorheol. Microcirc. 2018;69:101-14

945 women in the course of their pregnancy (n=1.259) and upto 1 week post partum (n=654)



Veränderungen vor SS bis 3. Trimenon

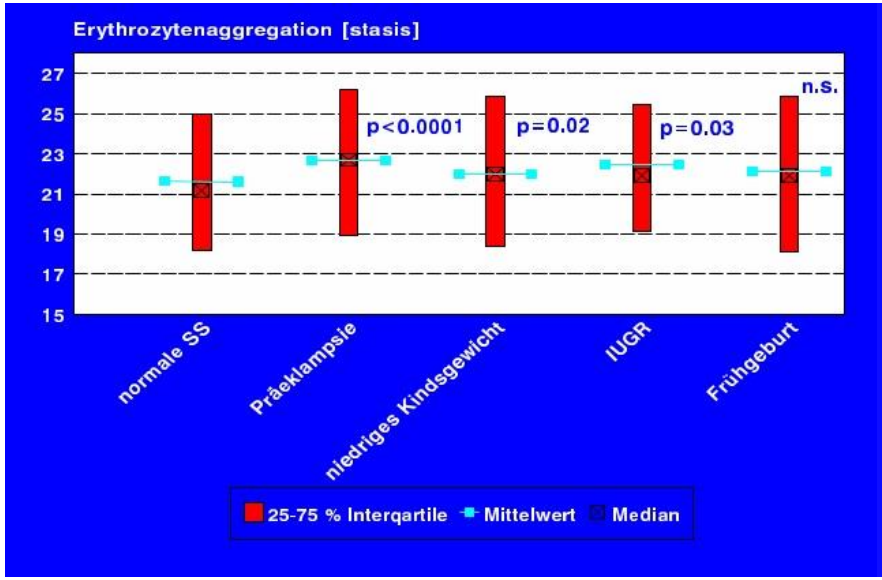
HCT:	- 9,0 %
RBC agg:	+ 30 %
RBC def:	- 5%
PV:	~ 0 %

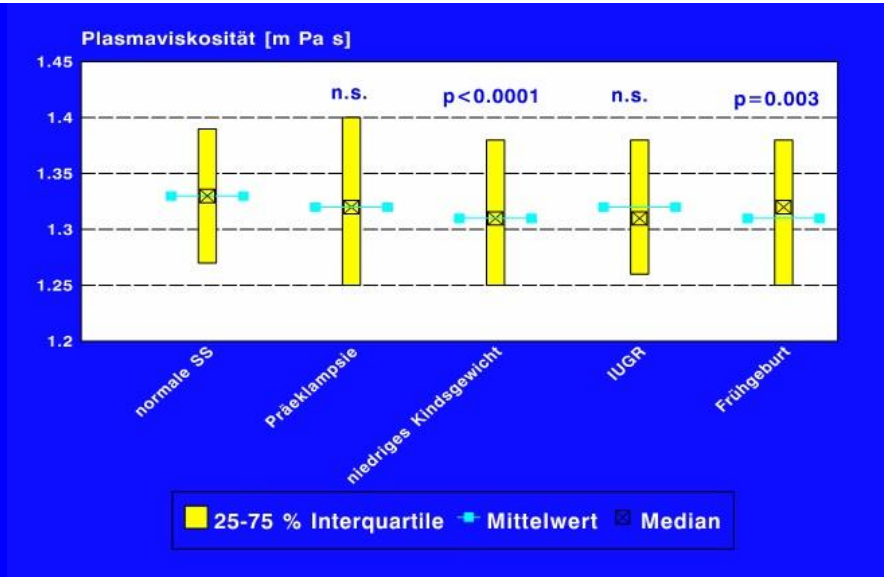
Blood Rheology at Term in Normal Pregnancy and in Patients with Adverse Outcome Events

von Tempelhoff GF Clin. Hemorheol. Microcirc. 2009; (Velten E, Inaugural Diss. 2008)

4,985 consecutively recorded singleton pregnancies at the time of their delivery

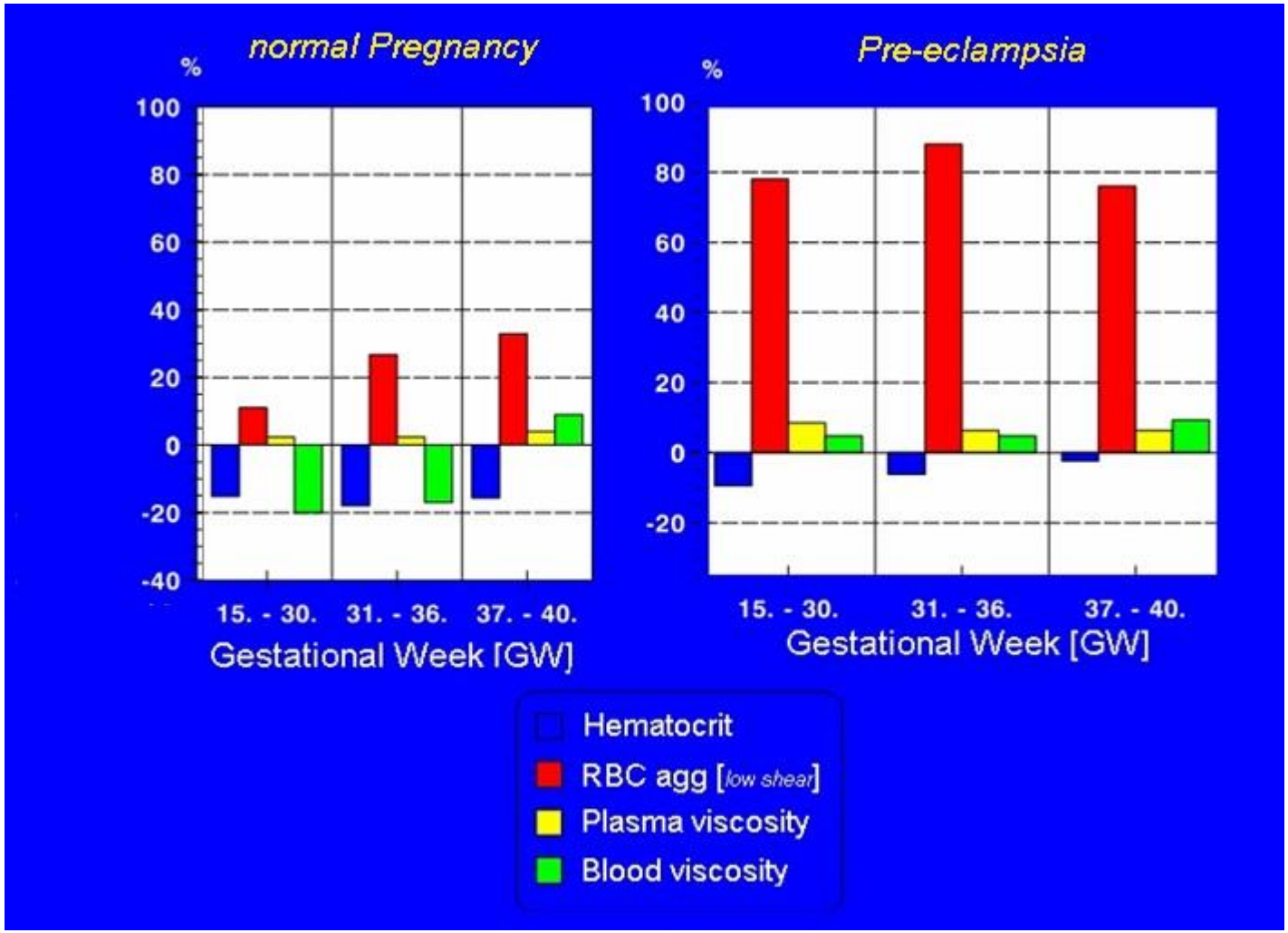
- Normal pregnancy ➔ **n = 3,959 (79.4 %)**
- Adverse outcome of pregnancy ➔ **n = 1,026 (20.6 %)**
  - Pre-eclampsia ➔ **n = 423 (8.4 %)**
  - Low birth-weight < 2,500 g ➔ n = 473 (9.5 %)
  - Early-birth < 37 GW ➔ n = 464 (9.3 %)
  - Intra uterine growth retardation (IUGR) ➔ n = 250 (5.0 %)





Blood Rheology during Normal Pregnancy and in Patients with Pre-eclampsia

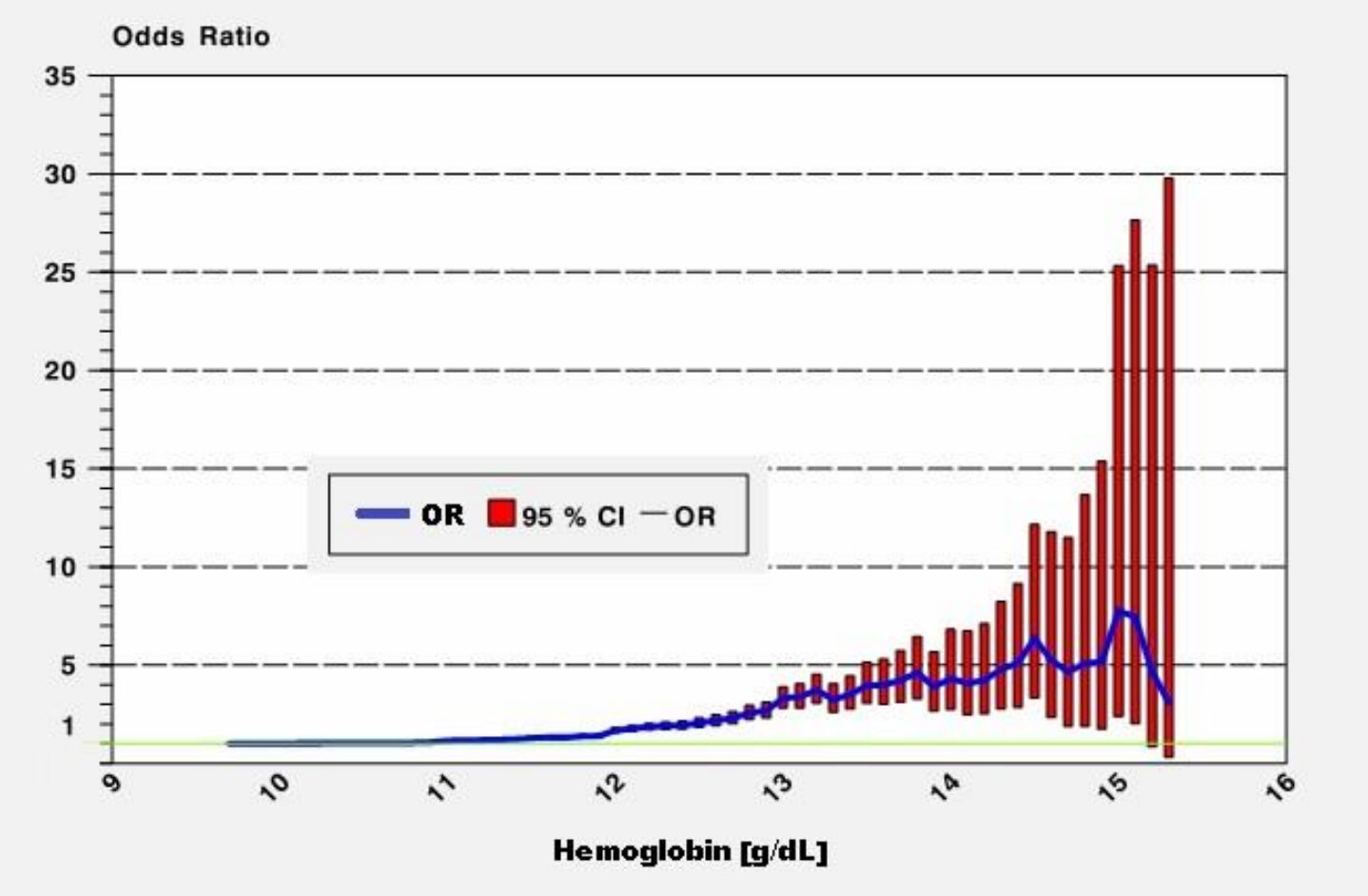
Heilmann et al. Bailliers Clin. Hematology 1987



Mean maternal 2nd trimester hemoglobin-concentration and outcome of pregnancy (n = 4.985) – A population based Study

von Tempelhoff et al. Clinical Applied Thrombosis/Hemostasis; 2009;14:19-28

Mean 2nd Trimester Hb and Risk of pre-eclampsia



Clarification in Patients with a History of severe Pre-eclampsia/HELLP - Syndrome

Clarification (not before 12 weeks after last pregnancy)

- **Acquired Blood Coagulation disorder:** ➔ APA-Syndrome
- **Immunologic testing:** ➔ Autoimmune diseases
  Lymphocyte **C**ytotoxicity **T**est

➔➔➔ Indication for IVIG in subsequent pregnancy

- **Blood Flow Properties:** ➔ Blood Rheologic Parameters
  Impedance Plethysmography
- **Blood Coagulation**: ➔ Thrombelastometry,
  in vitro Platelet - Function

Risk Factor in 46 Patients receiving IVIG for Prevention of recurrent Gestosis

History of Gestosis	**n = 46**	**100 %**
Antiphospholipid antibody – Syndrome	**n = 8**	**17 %**
Body Mass Index > 30 kg/m^2	n = 46	100 %
Pre exsisting Diabetes mellitus	n = 3	7 %
primipara (after Gestosis)	n = 38	83 %
Age > 40 Y	n = 6	13 %
Essential hypertension (before pregnancy)	n = 21	46 %
Ethnicity (afro-american)	n = 3	7 %

Autoimmune disease:	**n = 14**	**30 %**
APA-Syndrome	n = 8	17 %
Hashimoto	n = 5	11 %
ITP	n = 2	4 %
Celiac Disease	n = 1	2 %
Ulcerative colitis	n = 2	4 %
LCT < 25 %	**n = 36**	**78 %**

46 Women with a History of Pre-eclampsia / HELLP Syndrome (2016 - 2017)

Pre-eclampsia:	before gestational week 27	n = 6	(20 %)
(**n = 30; 100%**)	gestational week 27 and 36	n = 20	(67 %)
	after gestational week 36	n = 4	(13 %)
HELLP-Syndrome:	before gestational week 27	n = 14	(54 %)
(**n = 26; 100%**)	gestational week 27 and 36	n = 8	(31 %)
	after gestational week 36	n = 4	(15 %)
	One Episode:	n = 36	(78.3 %)
	Two Episode:	n = 10	(21.7 %)
	IUFT:	n = 8	

Controls: healthy pregnant women n = 257

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.

Blood Rheological Monitoring in Patients and Controls

Patients:

- Before each IVIG Cycle

Controls:

- when visiting for regular pregnancy check-ups.

Blood Rheological Monitoring during Pregnancy

- **Plasma viscosity:** (KSVP-1) Kapillarschlauch Viskosimeter
  Fresenius. Bad Homburg; Germany

- **RBC aggregation:** (MA1) Aggregometer
  Myrenne. Roetgen; Germany
  [*stase. low shear*]

- **RBC deformability:** Rheodyn SSD Scherstress-Diffraktometer
  Myrenne Roetgen; Germany
  24mPa S:

Def (low shear):	3.0
Def (moderate shear):	12.0
Def (high shear):	60.0

Characteristics of Patients and Controls

		Means	Standard deviation	Standard error	p-value
Age [Y]	patients	33.6	3.8	0.8	n.s.
	controls	35.1	4.7	0.3	
Weight [Kg]	patients	69.2	12.7	2.6	n.s.
	controls	70.5	13.9	1.1	
Height [cm]	patients	163.3	22.2	4.6	n.s.
	controls	167.1	9.9	0.7	
BMI [Kg/m^2]	patients	26.41	6.4	1.2	n.s.
	controls	26.03	12.2	0.9	

Results before Pregnancy in Patients (clarification-time) and Controls

		Mean	Standard deviation	Standard error	p-value
Hkt [%]	patients	39.3	2.2	0.69	n.s.
	controls	39.5	3.1	0.32	
PV [mPa s]	patients	1.17	0.05	0.01	n.s.
	controls	1.18	0.06	0.01	
E0 [S^{-1}] low shear	patients	15.0	4.49	0.92	n.s.
	controls	15.7	6.71	0.42	
E1 [S^{-1}] high shear	patients	17.9	5.30	1.08	n.s.
	controls	19.3	7.94	0.50	
Def low shear	patients	25.3	4.62	0.94	n.s.
	controls	24.7	5.38	0.35	
Def moderate shear	patients	41.1	5.97	1.22	n.s.
	controls	40.2	5.80	0.38	
Def high shear	patients	51.1	7.26	1.48	n.s.
	controls	50.3	5.93	0.39	

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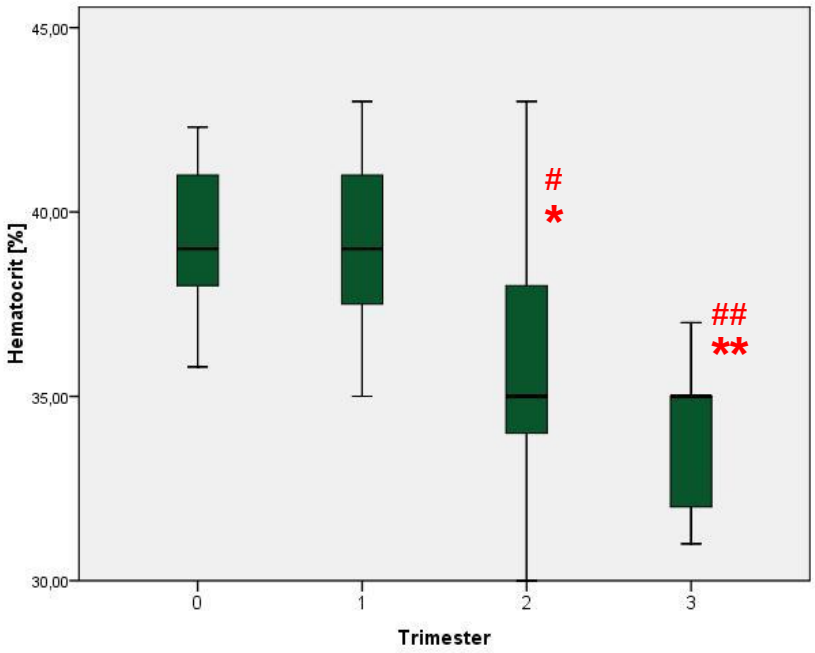
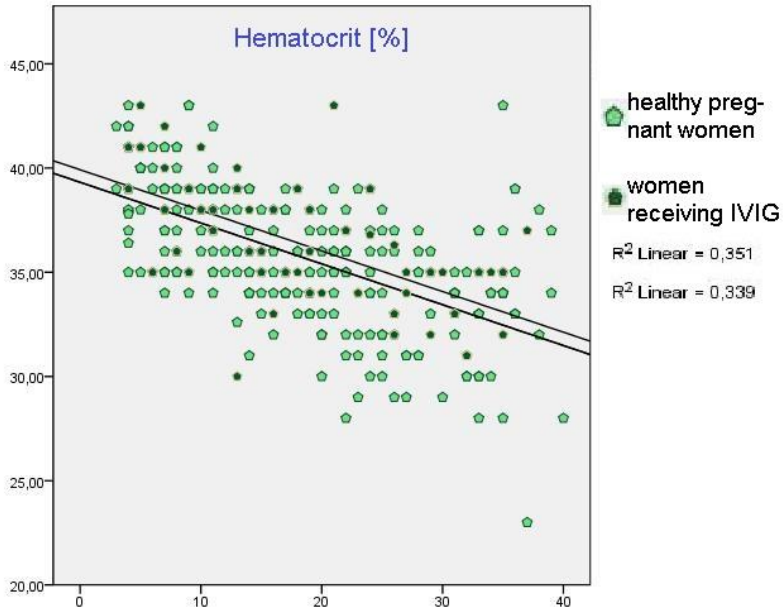
Hematocrit





0 ➔ time of clarification consultation (before next pregnancy)
1-3➔ Trimester: 1 - 3

Gestational week

0 vs. III ➔*: p<0.01; **: p<0.001
I vs. III: ➔#: p<0.01; ##: p<0.001

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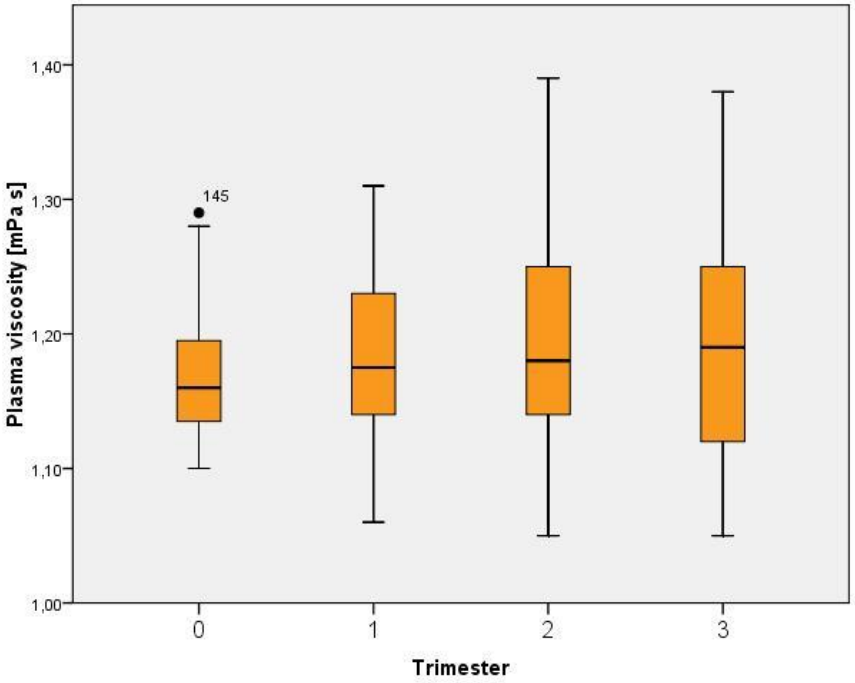
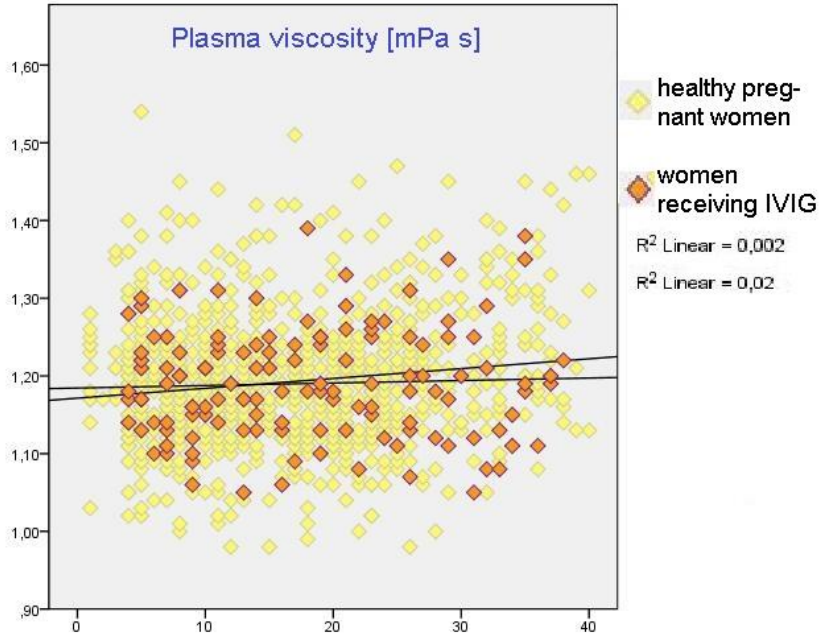
Plasma viscosity





Gestational week

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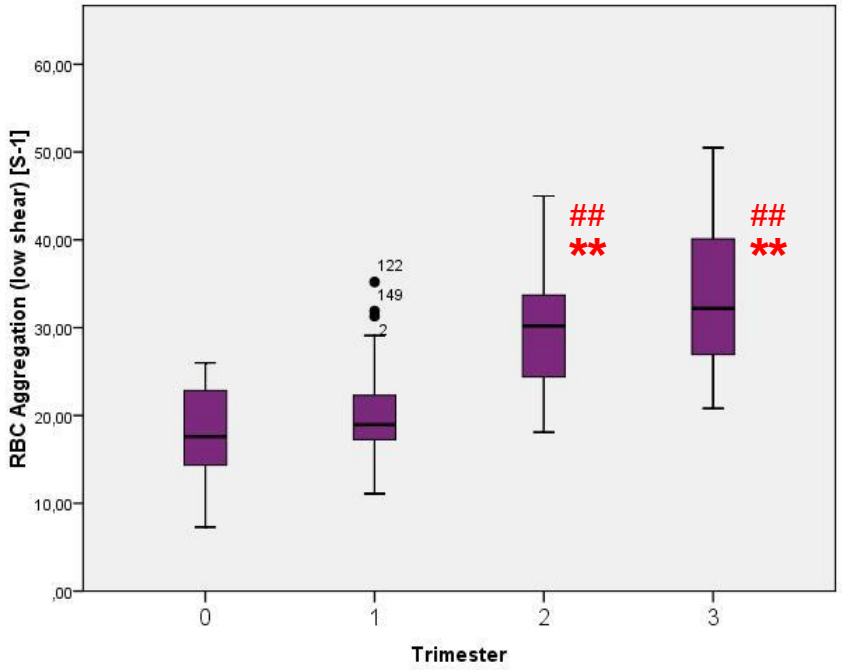
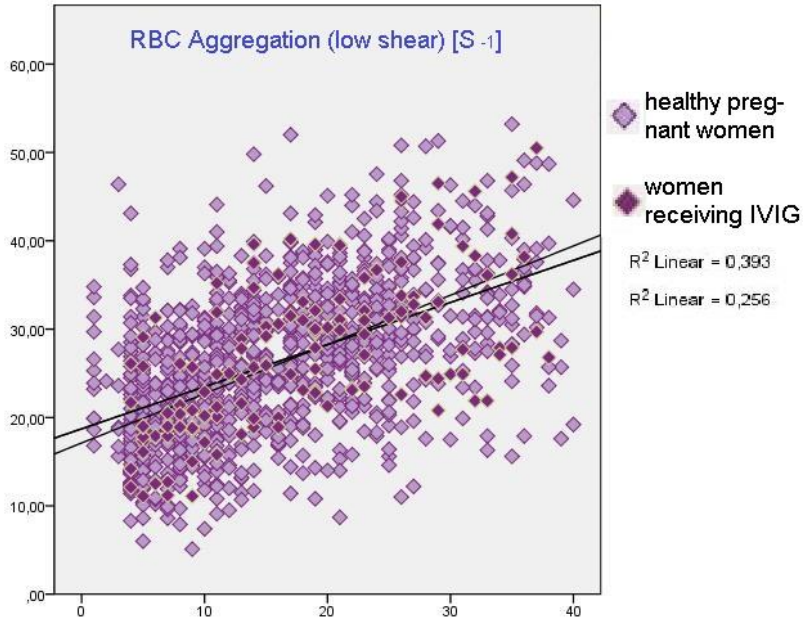
RBC Aggregation





0 ➔ time of clarification consultation (before next pregnancy)
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Gestational week

0 vs. III ➔*: p<0.01; **: p<0.001
I vs. III: ➔#: p<0.01; ##: p<0.001

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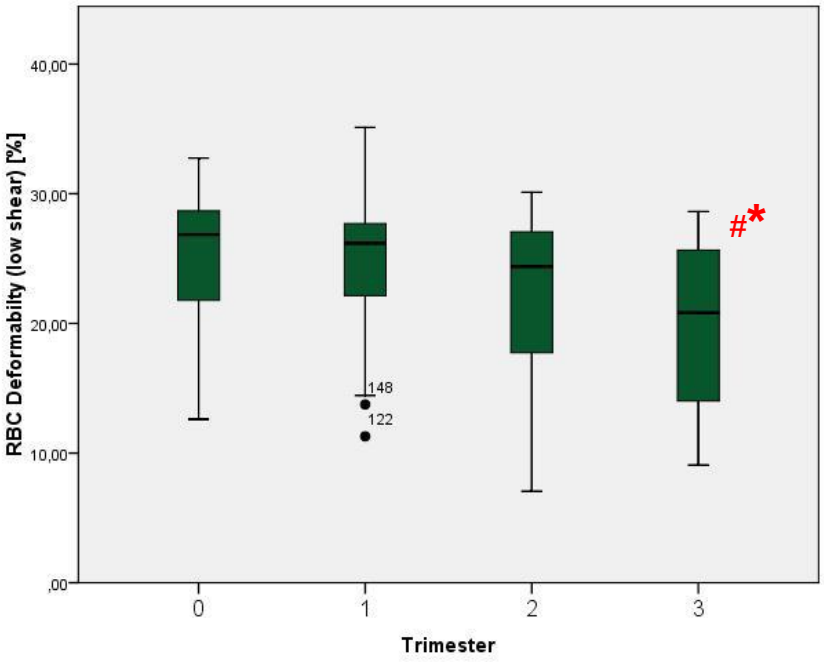
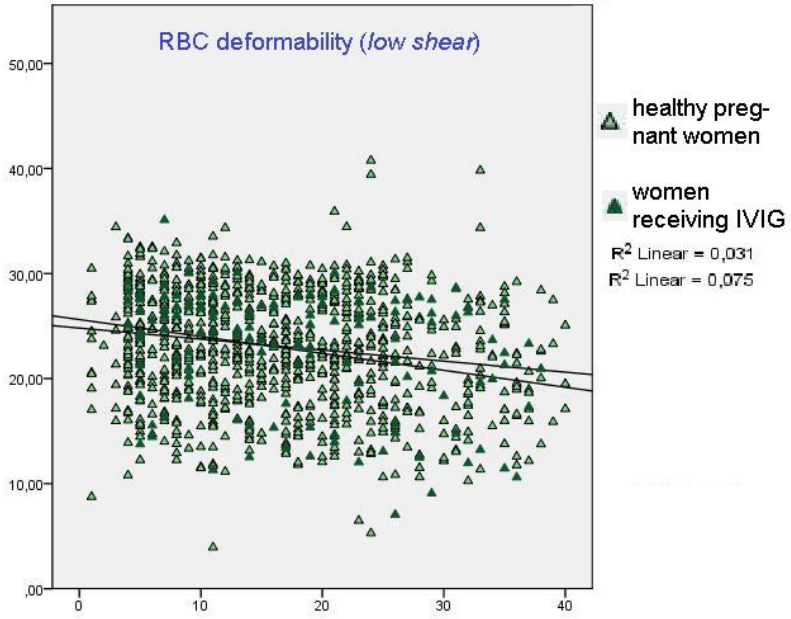
RBC Deformability (low shear) [%]





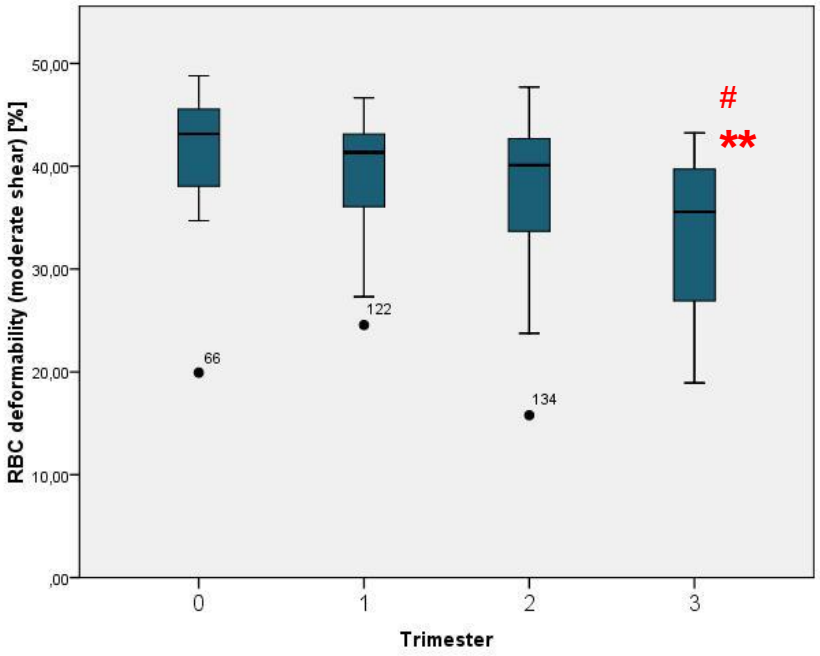
0 ➔ time of clarification consultation (before next pregnancy)
1-3➔ Trimester: 1 - 3

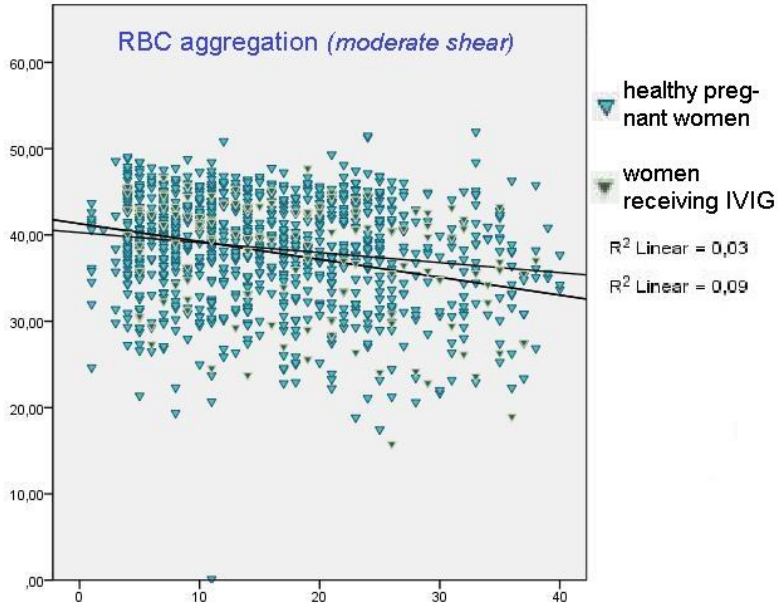
Gestational week

0 vs. III ➔*: p<0.01; **: p<0.001
I vs. III: ➔#: p<0.01; ##: p<0.001

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

RBC Deformability (moderate shear) [%]





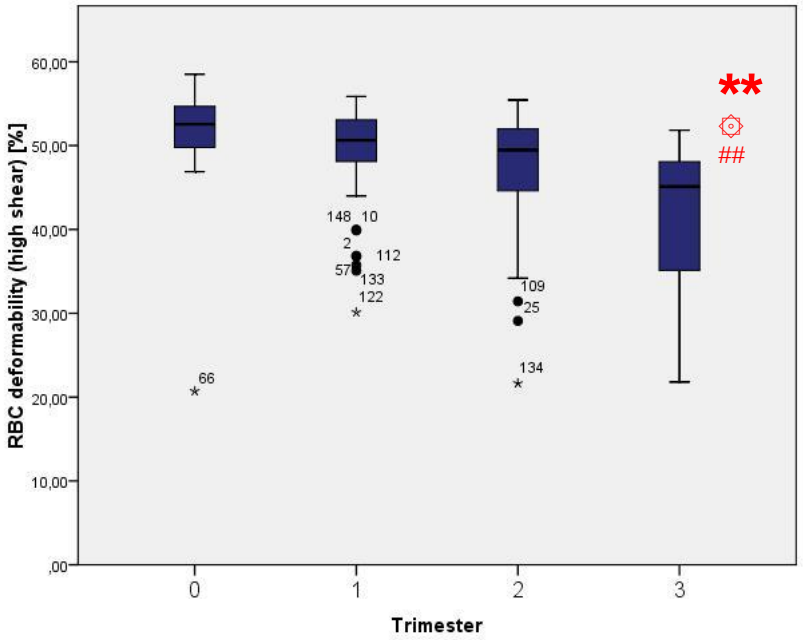
0 ➔ time of clarification consultation (before next pregnancy)
1-3➔ Trimester: 1 - 3

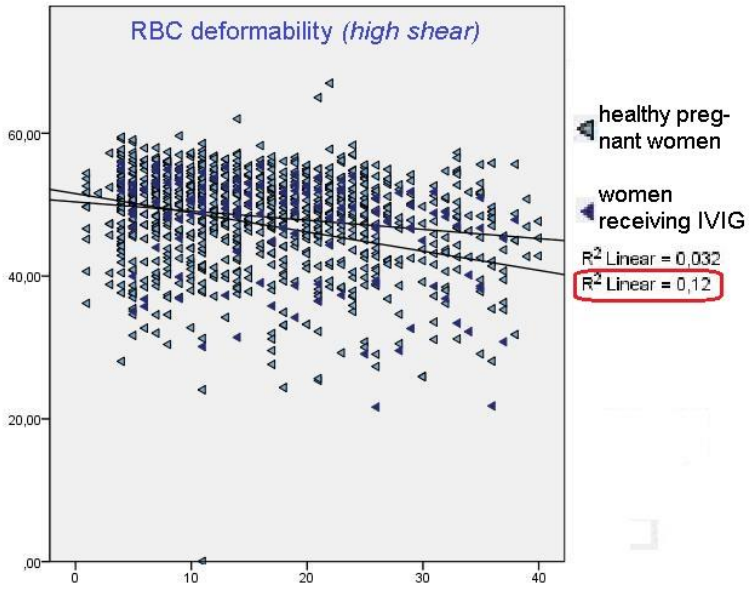
Gestational week

0 vs. III ➔*: p<0.01; **: p<0.001
I vs. III: ➔#: p<0.01; ##: p<0.001

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

RBC Deformability (high shear) [%]





0 ➔ time of clarification consultation (before next pregnancy)
1-3➔ Trimester: 1 - 3

Gestational week

0 vs. III ➔*: p<0.01; **: p<0.001
I vs. III: ➔#: p<0.01; ##: p<0.001
II vs III: ➔ ۞: p= 0.03

Outcome of Pregnancies after IVIG Treatment

- Life Birthrate: n = 37 (85 %)
- Mean GW at Delivery: 37 GW (Min: 26 GW / Max: 39 GW)
- Misscarriage: n = 9 (15 %)
- Uneventfull Pregnancy: n = 26 (58 %)
- Recurrent Gestosis: n = 3 (6 %)
- IUGR: n = 4 (4 %)
- IUFT / perinatal deceased: n = 0
- Early Birth (< 36. GW): n = 3 (6 %)
- Miscellaneous complications: n = 7 (15 %)

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Summary

- During IVIG treatment a significant reduction in the hematocrit is found from the beginning of pregnancy until delivery indicating a normal physiological hemodilution.
- Plasma viscosity remains unchanged during the course of pregnancy while RBC aggregation increases from the beginning of and throughout pregnancy.
- There is a constant decrease in RBC deformabilty under all shear rate conditions being most pronounced at term. However, compared to normal pregnancies under high shear rate the correlation between gestational age and trend of increase RBC rigidity is higher in women receiving IVIG.
- The patients number under investigation is too small as is the event-rate of adverse outcomes in order to compare blood rheological variables in sub groups such as patients according to their outcomes.

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Remark

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