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Foetale und maternale rheologische Parametern zum Zeitpunkt der Entbindung

Foetal and maternal rheological parameters at delivery

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Ziel der Dissertation / Fragestellung (Aim of the work)

Hemorheology is the science studying deformation and flow of blood. It has long been a science of pure academic interest generating many theories about blood flow in the microcirculation but not adding much to the laboratory routines in the clinical daily practice. There are however many clinical situations where rheological parameters are remarkably affected and consequently reflect the impact of the physiological and pathological changes in background. Pregnancy and child birth belong to these situations. Many changes take place in the female body from the moment she gets pregnant till the moment she gives birth, especially in the cardiovascular system. Birth is also a process that initiates huge changes in the fetus which transforms from an absolutely dependant living creature to an independent ever growing human being. Such a process necessitates drastic physiologic changes in all body systems.

Many published studies investigated the rheological changes during pregnancy and early neonatal life as well. In all those studies however, despite providing some cumulative evidence that rheological changes could significantly reflect physiologic and pathologic micro-vascular and functional changes during pregnancy and early neonatal life, solid evidence with enough statistical power could not be exclusively provided.

In this study, we investigated the rheological parameters in mothers and their newborns at time of delivery, correlated the rheological parameters of the mothers to the neonates and analyzed the variations in the rheological parameters in different normal and pathologic clinical situations both in pregnant women and their neonates.

Literaturdiskussion / Introduction

All fluids resist, to a greater or lesser extent, attempts to alter their shape, and this resistance to flow is a measure of a fluid's viscosity. During flow, as layers of fluid move parallel to one another at different rates, a velocity gradient develops between these layers and is known as the shear rate; it is measured in reciprocal seconds (s^{-1}). The force required to produce this velocity gradient is the shear stress and is measured in Newtons per square meter (Nm^{-2}). Viscosity can now be redefined as the ratio of shear stress to shear rate, the unit of viscosity being the Pascal second (Pa s) (1).

Hemorheology is the science of deformation and flow of blood. Blood is a heterogeneous medium that behaves during its flow as a non-Newtonian fluid where its viscosity depends on the conditions in which it flows. Blood viscosity increases exponentially at the low shear rates (below 50 s^{-1}) that characterize the venous blood flow. This increase is mainly caused by the larger molecular weight plasma proteins (fibrinogen and certain globulins) which bring the erythrocytes to stick together and form rouleaux; these large cellular aggregates cause a disproportionate increase in viscosity. At shear rates below 1 s^{-1}, alterations in plasma fibrinogen around the upper limit of the physiological range have a pronounced effect on whole-blood viscosity (Fig. 1) (1). At high shear rates, characterizing arterial flow (above 100 s^{-1}), red blood cell (RBC) rouleaux are dispersed, and individual erythrocytes are deformed into ellipsoids with their long axes aligned in the direction of flow, thus viscosity is relatively low, is virtually constant at high shear rates and is independent of the plasma fibrinogen (2,3). The appropriate shear-rate range corresponding to blood flow in capillaries is difficult to determine since the flow may be intermittent. When blood has become stationary, a relatively large force (the yield stress) is required to restart the flow once more, that is why there is uncertainty about the shear rates that characterize capillary blood flow and of the importance of measuring yield stress (1). In general, blood flow under high shear rates shows a flat flow profile while in small vessels with low shear rates shows a parabolic flow profile (4). In parabolic flow model, the highest shear rates exist in the laminas flowing near the vessel wall, while the mid stream lamina show lower shear rates, hence the parabolic flow pattern (4).

On the contrary to whole blood, plasma is a simple fluid that shows a linear relationship between shear stress and shear rate (i.e. Newtonian behavior of flow) so

that its viscosity remains constant at different shear stress values. Plasma viscosity correlates positively with increasing plasma fibrinogen and gamma globulins (5). Measurement of plasma viscosity is a useful screening test for detecting alterations in plasma proteins in acute and chronic disease (6) and has the considerable advantages of being unaffected by anemia, by age nor by sex of the patient (1).

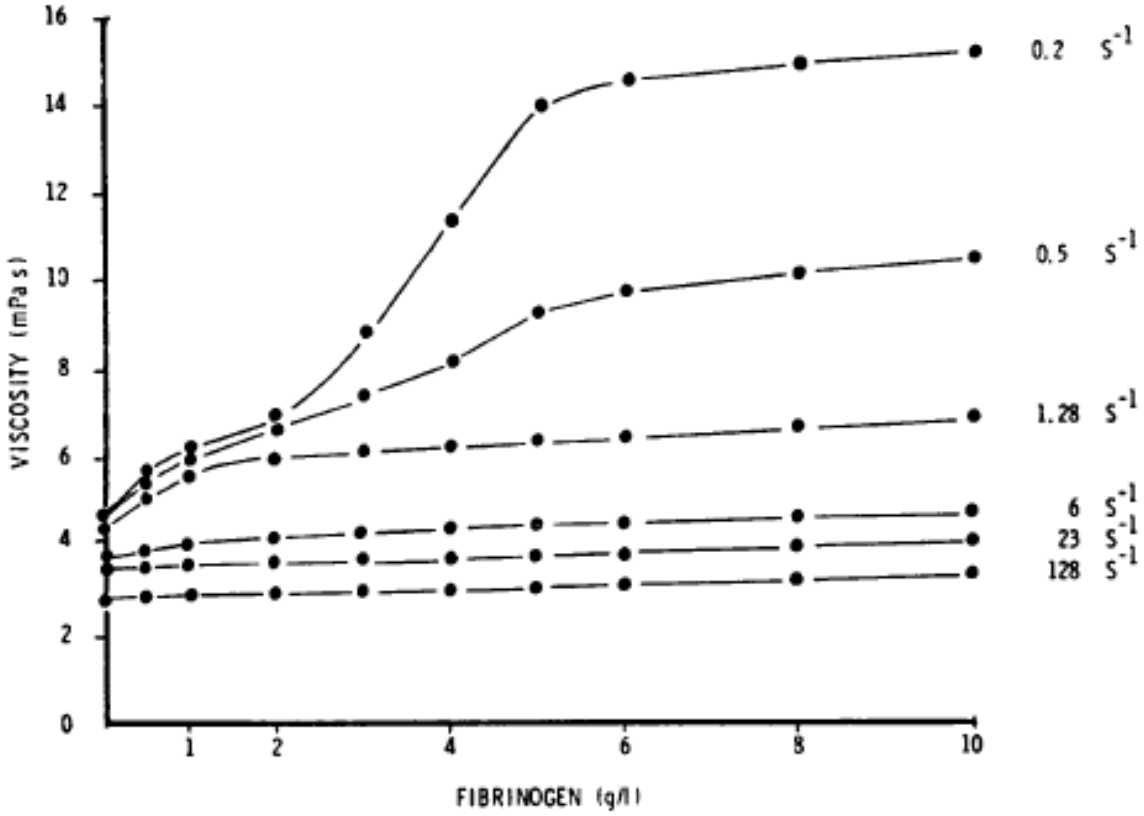

Figure 1 Disproportionate effect on blood viscosity at low, compared with high, shear of the addition of fibrinogen to washed red cells (1).

RBCs are the most abundant solid component of blood and play with plasma viscosity a major role in determining whole-blood viscosity. Within the physiological range there is a linear relationship between hematocrit (i.e. packed red cell volume) and the logarithm of whole-blood viscosity (7,8) making hematocrit the most important single determinant of whole-blood viscosity (1) but this relationship, however, is lost at very high and very low hematocrit values. This is clinically relevant in neonates, where the foetal / neonatal circulation is a high flow circulation characterized by low vascular pressures and low vascular resistance (9). At the same time, the normal range of hematocrit in the full term healthy newborn is between 45

and 65%. The newborn has thus a high flow / low resistance circulation with upper range hematocrit values, representing a different situation from the adult circulation (9), a fact that is put in consideration while going on with this study. The relatively poor sensitivity and specificity and the overdependence on the packed cell volume (i.e. hematocrit) have limited the clinical usefulness of whole-blood viscosity as a routine laboratory marker (10), thus plasma viscosity and erythrocyte aggregation are considered the important and reliable rheological parameters replacing whole-blood viscosity in clinical significance.

In order to analyze the significance of erythrocyte aggregation one has to understand the active forces and factors behind it. One of these important factors is the Zeta potential of RBCs, which is a potential energy barrier that prevents the RBCs from interacting with each other (11). Glycoproteins of the RBC membrane are responsible for the negatively charged surface which creates this repulsive electric potential between cells (12). Large molecular weight plasma proteins can overcome the red cell surface membrane zeta potential and exert their maximal effect on rouleaux formation and result in erythrocyte aggregation (13). Fibrinogen belongs to the plasma proteins with the greatest influence on the phenomenon of erythrocyte aggregation (1), thus erythrocyte aggregation can be considered as one of the rheological parameters reflecting plasma protein status and RBC membrane integrity.

The steps of the laboratory determination of different rheological parameters were reported by many authors using ever advancing armamentarium of laboratory equipment. The International Committee for Standardization in Haematology (ICSH) guidelines (14), despite the endless advancement in equipment, are usually followed by most of the studying groups to ensure providing comparable and reproducible test results that could be adopted reliably and with high credibility.

Evaluating blood and plasma viscosity is common part of investigating vascular disorders, like peripheral arterial disorders (15), diabetic microangiopathy (16) and to some extent ischemic heart disease (17). There also exists other clinical situations where rheological parameters are substantially affected and are of clinical relevance; pregnancy belongs to such situations. Pregnancy whether normal or abnormal goes along with marked vascular / hemodynamic changes, whereas rheological parameters are substantially affected. These changes are characterized by hypervolemia due to expanded plasma volume, a high cardiac output, a decrease in the vascular resistance and altered rheological parameters values namely plasma viscosity and erythrocyte aggregation both at stasis and under low shear forces

(18,19). The extent of plasma volume expansion can reach up to 40% (≈1,500 ml) more than the initial non-pregnant state and correlates significantly positive with foetal weight in normal pregnancy, reflecting the physiologic and clinical relevance of these cardiovascular changes to the pregnancy outcome (20-22). A comparative increase in red blood cell mass (≈500 ml) does not however occur, leading to a state of physiologic hemodilution. This hemodilution helps achieve an optimal pressure gradient for oxygen transport to the placental bed and hence to the foetus. The absence of hemodilution in the second trimester is clinically relevant, where a close correlation exists between the absence of this physiological process and the risk of development of pregnancy pathologies and complications (20,23,24).

Hemorheological parameters are not at all isolated from the physiological cardiovascular changes in pregnancy; the blood viscosity as a whole is reduced due to the physiological hemodilution of the pregnant state (25). In the low pressure system of the placenta, blood flow not only depends on blood pressure and vessel wall morphology, but also and to a marked extent on blood viscosity whose determinants are plasma viscosity, erythrocyte count (i.e. Hematocrit), aggregation and deformability (26). The studies investigating hemorheology in pregnancy are however controversial. Besides, most of the published studies included a small sample size that makes generalisation of their findings on the population almost impossible. As an example of this controversy, some published results on plasma viscosity values in pregnancy reported no change with gestation (26,27), some reported an increase (28,29), some a decrease (18), and others reported an initial increase followed either by no significant changes (30) or by a subsequent decrease (31).

Clinically, the blood flow changes during pregnancy could be demonstrated by the changes in the Doppler indices in the uterine vessels. The uterine artery Doppler flow patterns in normal pregnancy usually show absence of an end diastolic notch, which is normally present in non-pregnant states. The presence of this notch in the second trimester of pregnancy is a predictive marker for the development of preeclampsia later on in pregnancy (32-37). Poor conversion of uterine spiral arteries is the reason behind the increased uterine blood flow resistance (38), which is detected using Doppler ultrasonography. As mentioned above, blood flow under high shear stress (i.e. in arteries) is different from flow under low shear stress (i.e. in veins and in tissue capillaries), that is why it is possible to relate Doppler flow parameters to physio-

pathologic blood flow changes in arteries and big veins. Blood flow in arteries and relatively big vessels in general follows the Hagen-Poiseuille formula (39,40).

$$\dot{V} = \frac{dV}{dt} = \frac{\pi r^4}{8\eta}\frac{\Delta p}{l} = \frac{\pi r^4}{8\eta}\frac{\partial p}{\partial z}$$

The Hagen-Poiseuille's formula calculates the flow rate of a Newtonian fluid in a pipe (i.e. vessel) (V) at a constant temperature, which is directly proportional to the fourth power of the radius of this vessel (r), which is also directly proportional to the pressure gradient across the vessel (∆p) (i.e. between the vessel beginning and the vessel end). It is inversely proportional to the viscosity of the fluid flowing in the vessel (η) that is supposed to be constant in Newtonian fluids, and inversely proportional to the length of the vessel (l) (39,40). The same formula applies to blood flow in the big foetal vessels, like the umbilical and cerebral arteries. Umbilical artery Doppler flow indices reflect the velocity and the resistance to blood flow in the vessel. Giles et al. demonstrated a correlation between increased Doppler flow resistance indices in the umbilical artery and increased whole foetal blood viscosity accompanying increased foetal blood hematocrit. They could not however demonstrate a significant correlation between flow resistance and hematocrit under low shear rates, in other words, they could not correlate the increase in vascular resistance indices to hyperviscosity (41).

Rheological blood properties of newborns are markedly different from those of adults, with lower plasma viscosity and erythrocyte aggregation values recorded in the foetus (42,1). Among the studies investigating foetal and neonatal rheological parameters and their changes, comes the work of Mandelbaum et al., who found a correlation between plasma viscosity on one hand and cardiac output and vasodilatation respectively on the other hand when following neonates in the first five postnatal days. Plasma viscosity played a central role in the dynamic changes he validated. While whole blood viscosity remained constant, increasing plasma viscosity was the only foetal blood rheology marker that changed, going along with changes in Doppler flow indices in the first five postnatal days (43). Rheinhart et al. in their work, tried to clarify the factors influencing foetal blood rheology, through studying foetal and maternal whole blood viscosity. They found out that foetal whole blood viscosity did not differ from maternal whole blood viscosity. Moreover, they stated that when foetal and maternal blood were compared at the same hematocrit

(η_{p45}), the viscosity of foetal blood became significantly lower, by about 50% at shear rates below 1 s^{-1} and 20% at shear rates above 50 s^{-1}. However, they did not measure the actual values of plasma viscosity and hence they assumed that foetal plasma viscosity at term is lower than maternal plasma viscosity (44). The range of rheological parameters in healthy full term neonate was 0.988 – 1.132 mPa s for plasma viscosity (mean = 1.06, SD = 0.072 mPa s), 0.00 – 5.15 s^{-1} (mean = 2.41 SD = 2.74 s^{-1}) for erythrocyte aggregation at stasis and 2.13 – 14.89 s^{-1} (mean = 8.51, SD = 6.38 s^{-1}) for erythrocyte aggregation under low shear forces (45). When comparing this to maternal values at the time of delivery, in normal healthy pregnant women, plasma viscosity was 1.31 ± 0.09 m Pa s, erythrocyte aggregation at stasis was 21.6 ± 5.3 s^{-1}, and erythrocyte aggregation under low shear forces was 38.4 ± 7.9 s^{-1} (23). Thus absolute foetal blood rheological values are somehow lower than the corresponding values of the pregnant women. One of the main determinants of plasma viscosity is plasma protein concentrations and mainly Fibrinogen. Fibrinogen concentrations are lower in full term foetal blood than in adult blood and so is also plama viscosity (44). Fibrinogen concentration does not only affect plasma viscosity, but also affects erythrocyte aggregation and consequently whole blood viscosity under low shear rates of flow (1, 44), hence possibly explaining the lower foetal whole blood viscosity at term when compared to adult values (44). Other plasma protein fractions have of course an effect on plasma viscosity (44), and although immunoglobulins and acute inflammatory reaction proteins have the ability to stick to blood cell surfaces, and affect erythrocyte aggregation, they were not studied as possible determinants of blood rheology and foetal or maternal rheology parameters. Inflammatory conditions and conditions where immunoglobulins are substantially increased like Feto-maternal Rh-incompatibility or the less important ABO-incompatibility could be a very good example and a very good chance to study the effect of other plasma proteins on blood rheology.

Another very important determinant of foetal blood viscosity is erythrocyte deformability. Rheinhart et al. removed the plasma proteins, washed the foetal RBCs and through this could demonstrate that the low viscosity under low shear rates had vanished or was even reversed, reflecting an independent effect of foetal RBC deformability on the whole blood viscosity (44). Increased foetal erythrocyte deformability was demonstrated by Eguchi et al. stating that foetal erythrocyte deformability is increased even to match non pregnant levels (46).The reasons behind this finding were however not validated (44), and could be due to the different

viscosity characteristics of foetal hemoglobin filling the foetal RBCs in comparison to adult hemoglobin.

The aforementioned studies however, dealt with the foetal blood rheology as an independent finding, and did not try to relate foetal blood rheological parameters to those of the mother or to investigate the effect trans-placental transfer on blood rheology on both sides.

The human placenta is a hemochorial organ, where a direct physical contact occurs between the maternal blood and the chorionic trophoblasts in order to achieve the targeted interaction between the two circulations (i.e. foetal and maternal) (47). The foetal blood flows in the chorionic villi that bathe in maternal blood stagnating in the inter-villous spaces. The inter-villous spaces form an interlacing network of cavities and lacunae and contain maternal blood being poured with low pressure through the spiral arteries. Foetal blood and maternal blood are separated by zygote generated trophoblastic cell layers (48). This is the cellular structure that controls foetal-maternal transport. The placenta controls fluid, electrolyte, protein and cellular transport between the foetal and the maternal circulations. Burton et al. studied the physiological and rheological aspects of blood flow in the uteroplacental unit and set a theoretical model to study the blood flow in the maternal inter-villous spaces in normal pregnancies and cases with absent conversion of the spiral arteries. The spiral arteries show normally a wave of invasion of foetal trophoblasts in the first trimester, then a second wave of invasion around the 20^{th} week of gestation. The invading trophoblasts convert the spiral arteries into muscle-free thin walled vessels that allow blood to flow into the maternal inter-villous spaces with a slow velocity, where the normal determinants of blood flow according to Hagen-Poiseuille law like the vessel diameter and pressure gradient across the vessel play a minimal role in determining the characteristic of flow, and the blood viscosity plays rather the main role in controlling blood flow (49). Absence of this spiral arteries conversion is correlated to development of preeclampsia, foetal growth retardation and guarded pregnancy outcome in general (50-53). Burton and his study group’s model showed that in the absence of conversion blood will enter the intervillous space as a turbulent jet at rates of 1–2 m/s. They speculated that the high momentum will damage villous architecture, rupturing anchoring villi and creating echogenic cystic lesions as evidenced by ultrasound. The retention of smooth muscle will also increase the risk of spontaneous vasoconstriction and ischaemia–reperfusion injury, generating oxidative stress. Dilation has a surprisingly modest impact on total blood flow, and so

they hypothesized the placental pathology associated with deficient conversion is dominated by rheological consequences rather than chronic hypoxia (49).

In the course of pregnancy many disorders develop and many situations are encountered that deviate from the norm, and many of these situations have a proven impact on hemorheologic characteristics. Smoking belongs to these situations. Preterm labor is also a main contributor to neonatal mortality, and it was long proven that corticosteroid prophylaxis has a substantial protective effect against the development of many unwanted complications of prematurity. At the end, comes Iron supplementation which is one of the most common situations encountered during normal pregnancy. We find this issue important, because hematocrit and hemoglobin concentrations are parts of the blood rheology parameters and are influenced by iron blood levels and iron intake. Besides, it is estimated that 41.8% of the pregnant women worldwide are anemic, most of them reside in under developed countries (54). Moreover, a survey in 46 countries showed that 52% to 75% of mothers receive a form of iron supplementation during pregnancy and the duration is usually short (55), reflecting the frequency of iron intake during pregnancy and its impact on maternal health and possible impact on maternal and foetal blood rheology. That is why we studied the effects of these situations on foetal blood rheology.

Smoking is a known cardiovascular risk factor and a carcinogen. It has been thoroughly studied for decades regarding its adverse effects and various health risks. The effect of smoking on blood rheology has not been that much investigated, especially in pregnant women and above all the effect on the rheological characteristics of the newborn. Smoking results in a significant increase in whole blood viscosity in adults (56). As a consequence, one expects an effect of smoking on the placental circulation. Machado et al. in their study on the effect of smoking on maternal-foetal circulation and the dose dependant effect of smoking, used Doppler velocimetry values to study the uterine artery flow on the maternal side, the umbilical and the middle cerebral arteries flow on the foetal side. They demonstrated through their work significantly higher resistance indices when comparing smoking to non smoking pregnant women. A dose-dependent effect in placental blood flow was found where the resistance indices increased in accordance with increasing levels of tobacco smoking exposure. In addition, a decrease in foetal birth weight also correlated to increasing tobacco consumption was demonstrated (57). An appropriate study on the exact effects of smoking during pregnancy on the fetus, the foetal

microcirculation or the foetal rheology is still missing, what we have are small studies whose result are going to be critically appraised against the results of our work.

Preterm labor is a worldwide problem where 11.1% of the babies born worldwide are estimated to be preterm (58). Prematurity is the most common cause of mortality in infants (59). Corticosteroid prophylaxis for preterm birth significantly reduces the incidence of respiratory distress syndrome, intra-ventricular hemorrhage and necrotizing colitis (60, 61). The effect of corticosteroid prophylaxis on the pregnancy outcome was thoroughly investigated, but its effect on the rheological parameters in the mother and the fetus have not been investigated thoroughly. This might be an interesting issue because corticosteroids have significant effects on the micro-cellular environment through their wide spread effects on inflammatory proteins, cellular permeability and water and electrolyte balance.

To sum up, rheological findings in neonates are not thoroughly studied as it is with adult rheology. Moreover, hemorheologic conditions in mother and neonates may be viewed as two independent systems, since a steady, although not unrestricted Maternal-foetal exchange in the inter-villous space of the placenta takes place that likely influences blood rheology and supply in neonates.

Material und Methoden (Patients and methods)

This was a retrospective cross-sectional observational study that included healthy pregnant women with singleton conception who presented first at completed 26 weeks and until completed 43 weeks of gestation. The files of all the pregnant women who completed 26 weeks' gestation and admitted to the labor and delivery ward of the Women's Hospital of the City Hospital of Rüsselsheim, in the time period from January 1990 to the end of December 1996 and who met the above mentioned inclusion criteria, were included into this retrospective investigation. Maternal data was routinely registered in the files by the attending physicians at that time, namely age, body mass index (BMI), duration of pregnancy in weeks and if corticosteroid prophylaxis, due threatening preterm labor, was given in pregnancy or not. This data was obtained from the maternal log (Mutterpass), in addition, the maternal intake of iron supplementation during pregnancy and smoking were sought as well. The data was routinely registered in the patients' files as standard of care.

As regards the neonates, we included in our analysis the neonates of the recruited mothers, who were healthy full term, and preterm newborns as well. The birth weight and gestational age at birth were registered and if the mother received corticosteroid prophylaxis earlier in pregnancy or not.

All the aforementioned data in addition to the results of the laboratory examinations were registered and stored in the patients' files by the attending physicians in the women's Hospital of the city hospital of Rüsselsheim at that time. This was done by the attending physician whether during the working hours or on duty and on weekends and official vacations as well. The laboratory examinations were performed by a laboratory technician who was financially supported through the third-party funds account of the Rüsselsheim City Hospital.

This invaluable database was further used in other publications and dissertations with other aims and primary end points.

The candidate did not share in the active data registration or storage phase and was not involved in the direct medical care of the pregnant women or involved in attending the delivery, however the candidate has anonymously digitalized the corresponding data stored in the patients' files, who were recruited into this study, tabulated it in a suitable form and did the statistical analysis.

Rheological parameters:

I The fetus

I.1 Blood sampling technique

Umbilical cord blood was obtained directly after the cord has been cut, by the physician attending the delivery. After minimal stasis of the blood in a small segment of the clamped and already transected umbilical cord at the maternal side, blood was drawn from the umbilical vein using a 20 gauge needle supplied with a vacuum tube (Sarstedt, Nümbrecht-Rommelsdorf, Germany).

I.2 Plasma viscosity

Blood was collected in vacuum tubes containing 1:10 potassium EDTA (ethylene diamine tetraacetic acid) and rheological estimations were immediately performed in the laboratory of the department of gynecology & obstetrics according to ICSH guidelines (14).

Since plasma behaves as a Newtonian fluid, the shear rate at which its viscosity is measured is not critical. Thus a simple capillary viscometer, in which the shear rate is not only non-physiologically high but also varies across the lumen of the tube, may be used. Viscosity is determined by the time taken for the test plasma to flow through a capillary tube at controlled temperature. The latter must be kept constant, since viscosity is highly dependent on temperature, although the actual temperature selected is not critical. In this study, for determination of plasma viscosity, the blood-EDTA mixture contained in vacuum tubes was centrifuged for 20 minutes (2000g at 4◦c) whereas probes from the middle-layer of the plasma were obtained, and after the air blisters are evacuated the probes were inserted into and measured with the system of a capillary tube viscosimeter (KSPV 1 Fresenius, bad homburg Germany) at 37◦c according to Jung et al (62) (normal adult range: 1.14– 1.34 m pa) (Fig. 2). The apparatus digitally generates the plasma viscosity readings in mPas. The measurements accuracy were calibrated before beginning plasma viscosity estimations and was repeated when needed. (23).

I.3 Erythrocyte aggregation (at stasis and under low shear forces)

Red blood cell aggregation was estimated using a photometric rheoscope developed by Schmid- Schoenbein et al (63) (Fig. 3). Average RBC aggregation is determined by the quantity of light transmission which is measured by photo sensors in two modes, during stasis and while samples are subjected to low shear rate of 3 s−1. Light transmission increases proportionally with extended RBC aggregation. The data are then processed by an integrated computer and expressed in arbitrary units (s^{-1}). The EDTA-containing blood sample is centrifuged for 10 minutes at 300 U/min so that a suspension of erythrocyte in its own autologous plasma is produced corresponding to a hematocrit level of 45%. 20 µL of this sampe is then placed into the Myrenne Aggregometer (Myrenne, Roetgen, Germany).

Figure 2. The KSPV 1 apparatus (62).

Figure 3. MA 1 Myrenne Aggregometer (63,64).

I.4 Hematocrit

Hematocrit level measurement was performed using the Coulter Counter R, Modell S 880 apparatus (Coulter Electronics GmbH, Krefeld, Germany).

II The mother

Estimations of blood rheological parameters were performed at the time of admission into the labor and delivery ward and were repeated every 24 hours until delivery. Only the last estimations value was included in our records thus calculations are based on the results within a time-range of maximum 24 hours prior to delivery.

II.1 Blood sampling technique

The maternal blood samples were obtained by the attending physician. After minimal stasis of the upper arm blood was drawn from the antecubital vein using a 20 gauge needle supplied with a vacuum tube (Sarstedt, Nümbrecht-Rommelsdorf, Germany). Blood was collected in vacuum tubes containing 1:10 potassium EDTA (ethylene diamine tetraacetic acid) and rheological estimations were immediately performed as described above in the foetal section.

Statistical analysis:

Descriptive analysis included mean values ± standard deviations, median, inter quartile range. Differences between the means of different groups were assessed using the one-way analysis of variation (ANOVA) test. Two sided Pearson's correlation coefficient was used to correlate different parameters. P values of less than 0.05 were considered statistically significant. All tests are performed with assuming a confidence interval of 95%. Statistical analyses were conducted using PSPP-project version 0.7.9, released February 2012.

Ergebnisse (Results)

This is a retrospective cross-sectional observational study concerning patients' data who gave birth in the period from January 1990 until December 1996, in the Women's Hospital of City Hospital of Rüsselsheim. During this period information from 5,033 pregnant women presenting at delivery and their newborns was stored. Among those deliveries 4,985 patients had a singleton pregnancy, and those were the deliveries that met the inclusion criteria of our study. According to the maternal log data and the clinical findings at admission to the delivery room, we included data from those 4,985 pregnant women and their newborns. Table 1 shows the numbers of smoking mothers versus non-smoking ones, the number of mothers who received corticosteroid prophylaxis during pregnancy versus those who did not and the number of mothers who received iron supplementation during pregnancy versus those who did not.

Table 1. Patients' characteristics of our cohort.

	N (patients)
Neonates to smoking mothers	698
Neonates to non-smoking mothers	4242
Neonates to mothers who received corticosteroid prophylaxis	216
Neonates to mothers who did not receive corticosteroid prophylaxis	4706
Neonates to mothers who received iron supplementation	406
Neonates to mothers who did not receive iron supplementation	4534

Correlation between neonatal blood rheological parameters and maternal clinical characteristics

In this study the maternal age showed no statistically significant correlation to foetal haemoglobin, hematocrit and plasma viscosity. However, it showed a negative weak correlation, which was statistically significant, for both foetal erythrocyte aggregation at stasis and under low shear forces. Maternal weight at delivery showed a weak correlation to foetal haemoglobin concentrations and hematocrit which was statistically significant, the correlation to erythrocyte aggregation at stasis and low shear forces was weak negative but still statistically significant. Foetal plasma viscosity was not statistically significantly correlated to maternal weight at delivery. BMI was also in turn weakly correlated to all haematological and rheological parameters, only the correlation with hematocrit and erythrocyte aggregation at stasis was statistically significant. These results are elaborated in Table 2.

Table 2. Correlation of clinical maternal characteristics and rheological parameters in foetal blood.

Foetal / **Maternal**		**Hb**	**Hct**	**Pv**	**E0**	**E1**
Age	**N**	4908	4907	4850	4865	4835
	r	0.018	0.017	-0.027	-0.034	-0.037
	p	0.209	0.230	0.056	**0.018***	**0.011***
WD	**N**	4940	4939	4882	4869	4840
	r	0.061	0.067	0.024	-0.032	-0.037
	p	**<0.0001***	**<0.0001***	0.099	**0.025***	**0.009***
BMI	**N**	4919	4918	4863	4723	4 693
	r	0.028	0.033	-0.003	-0.041	0.009
	p	0.053	**0.022***	0.847	**0.005***	0.528

N is the number of studied observations, * is a statistically significant p value ($p<0.05$). r is Pearson's correlation coefficient. Hb = haemoglobin, hematocrit = haematocrit, Pv = plasma viscosity, E0 = erythrocyte aggregation at stasis, E1 = erythrocyte aggregation under low shear forces, WD = maternal weight at delivery and BMI is body mass index.

Correlation between neonatal and maternal hemorheological and hematological parameters.

The maternal hematocrit and haemoglobin both were statistically significantly positive correlated with foetal haemoglobin, hematocrit and plasma viscosity, while showed statistically significant negative correlation to foetal erythrocyte aggregation at stasis and erythrocyte aggregation under low shear forces. Though these cited correlations were statistically significant yet the correlation between maternal and foetal haemoglobin and hematocrit were far stronger as the other observed correlations. The maternal plasma viscosity was statistically significantly positive correlated with the foetal hemoglobin, hematocrit and foetal plasma viscosity, whereas the latter was strong for maternal and foetal plasma viscosity. In contrast, maternal plasma viscosity was correlated statistically significant negatively to foetal erythrocyte aggregation at stasis, though it was a weak correlation. The correlation between maternal plasma viscosity and foetal erythrocyte aggregation under low shear forces was both very weak and anyway not statistically significant. Maternal erythrocyte aggregation at stasis was statistically significant positive correlated to most of the foetal rheological parameters namely foetal hematocrit, foetal plasma viscosity and to erythrocyte aggregation at stasis and under low shear forces as well. Maternal erythrocyte aggregation under low shear forces was also statistically significant positive correlated to foetal haemoglobin, foetal haematocrit, foetal erythrocyte aggregation at stasis and under low shear forces. It was however statistically significant inversely correlated to foetal gestational age at delivery. Although the correlations between maternal erythrocyte aggregation both at stasis and under low shear forces and the different foetal rheological and haematological parameters were mostly statistically significant yet the correlation coefficient for all those observed correlations was obviously weak. These correlations are showed in table 3.

Table 3. Correlation of maternal and foetal rheological characteristics.

Foetal / **Maternal**		**Hb**	**Hct**	**Pv**	**E0**	**E1**
Hct	**N**	4911	4910	4854	4865	4835
	r	0.144	0.143	0.059	-0.034	-0.037
	p	**<0.0001***	**<0.0001***	**<0.0001***	**0.018***	**0.011***
Hb	**N**	4915	4914	4857	4869	4840
	r	0.144	0.143	0.053	-0.032	-0.037
	p	**<0.0001***	**<0.0001***	**<0.0001***	**0.025***	**0.009***
Pv	**N**	4762	4761	4745	4723	4 693
	r	0.089	0.088	0.200	-0.041	0.009
	p	**<0.0001***	**<0.0001***	**<0.0001***	**0.005***	0.528
E0	**N**	4746	4745	4697	4722	4692
	r	0.026	0.029	-0.035	0.077	0.057
	p	0.078	**0.043***	**0.018***	**<0.0001***	**<0.0001***
E1	**N**	4767	4766	4718	4743	4713
	r	0.054	0.051	-0.005	0.040	0.055
	p	**<0.0001***	**<0.0001***	0.730	**0.006***	**<0.0001***

N is the number of studied observations, * is a statistically significant p value ($p<0.05$). r is Pearson's correlation coefficient. Hb = haemoglobin, hct = haematocrit, Pv = plasma viscosity, E0 = erythrocyte aggregation at stasis, E1 = erythrocyte aggregation under low shear forces.

A dot scatter diagram graphically representing the distribution and the correlation of maternal and foetal erythrocyte aggregation is shown in Figure 4.

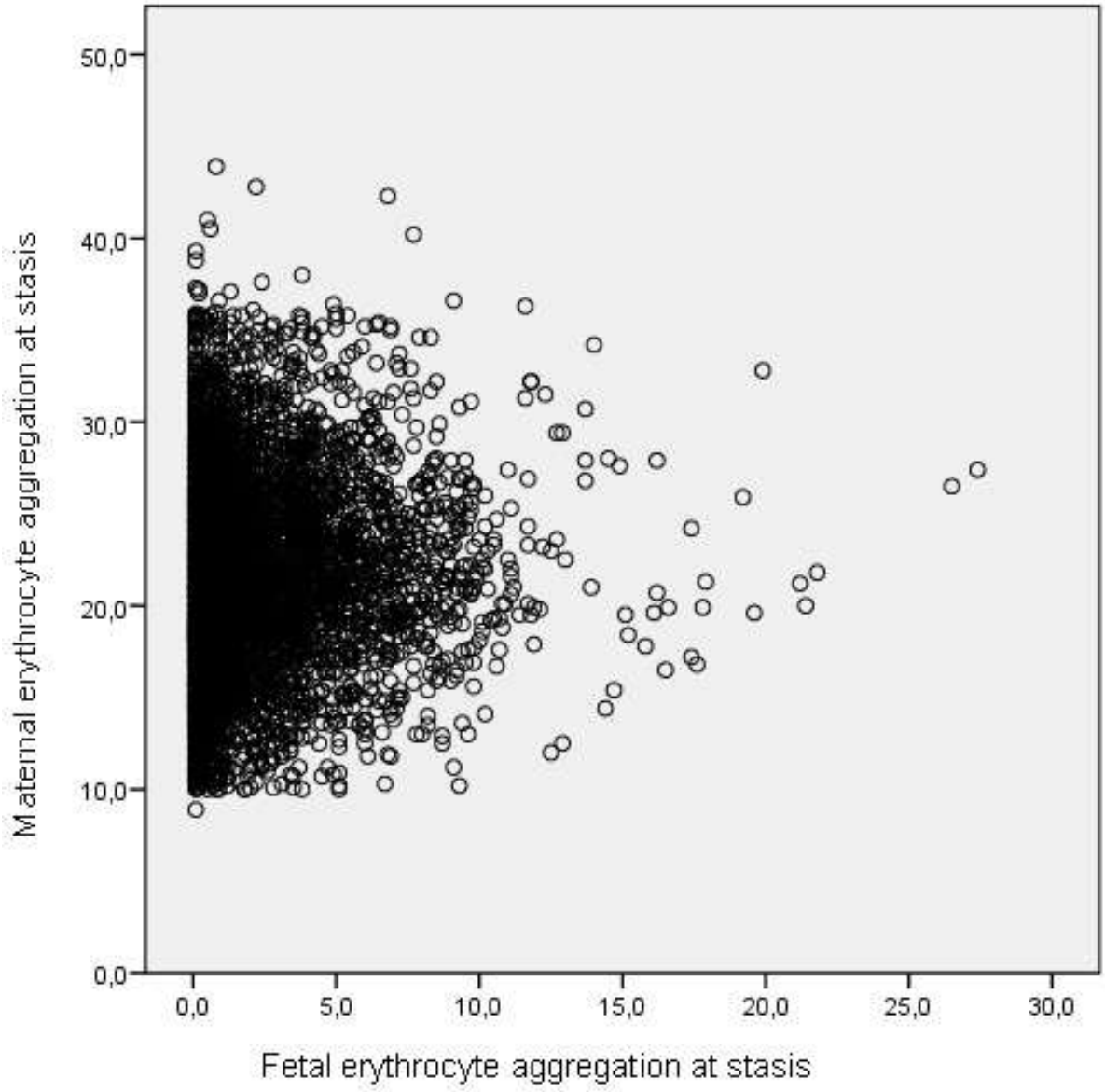

Figure 4. Scatter diagram correlating foetal to maternal erythrocyte aggregation at stasis. (r = 0.077, p < 0.0001). In this Figure, 50% of the maternal values were scattered between 15 and 30 s^{-1} with a bell shaped distribution pattern, while foetal erythrocyte aggregation at stasis was scattered between 0.1 and 5 s^{-1} indicating a left listed distribution with lower values when compared to the maternal ones.

The scatter diagram shows the values of erythrocyte aggregation at stasis at both the maternal and foetal sides and their stretch over a wide range of values reflects the weak calculated value of Pearson's correlation coefficient (r = 0.077). The high density of the scatter diagram reflects the large number of samples included in the study.

Analysing the correlation of the maternal and foetal erythrocyte aggregation under low shear forces, figure 5 represented the statistic results eloquently.

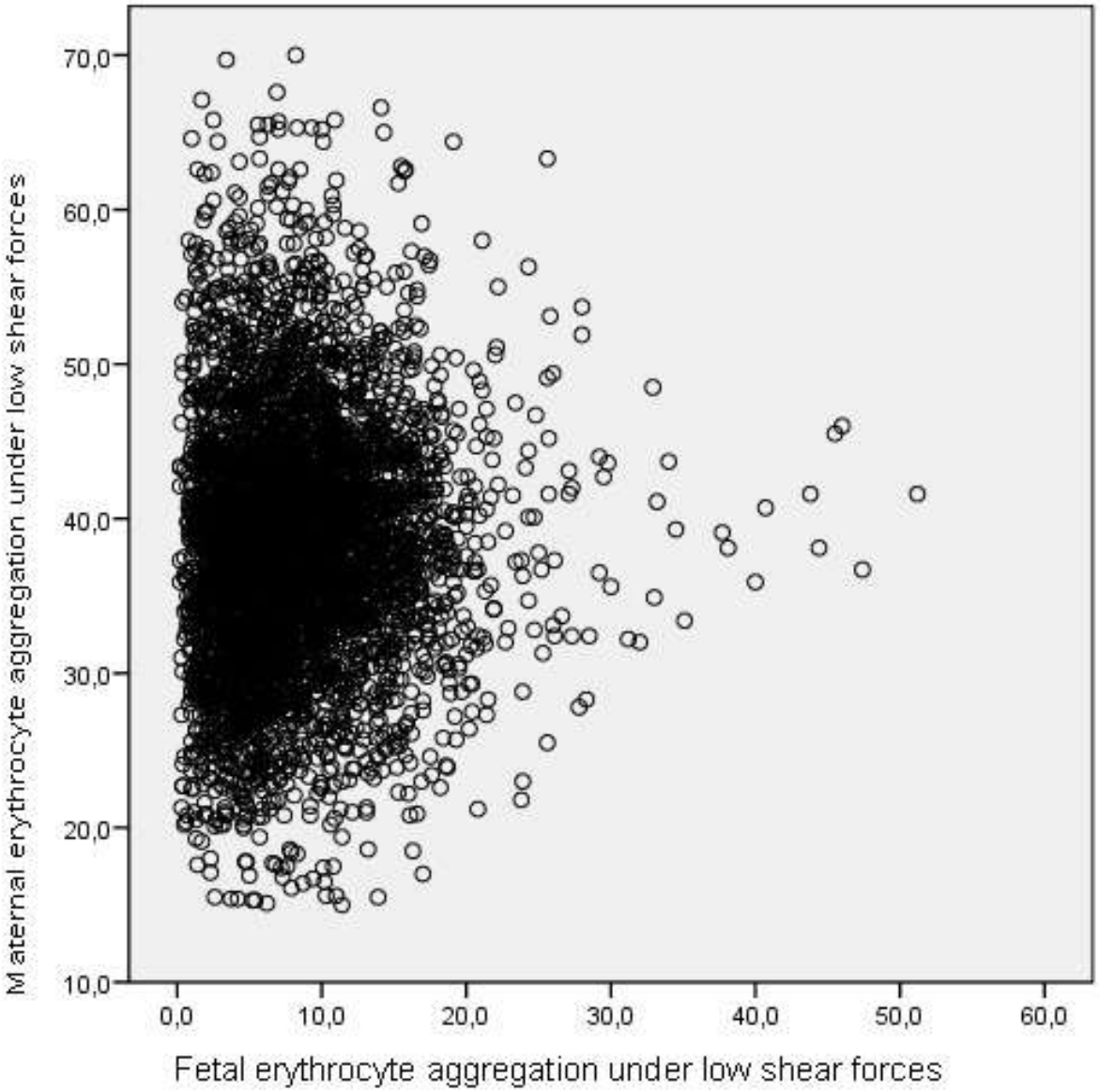

Figure 5. Scatter diagram correlating foetal to maternal erythrocyte aggregation under low shear forces. ($r = 0.055$, $p < 0.0001$). 50% of the maternal values were scattered between 30 and 43 s^{-1} with a bell shaped distribution pattern, while foetal erythrocyte aggregation under low shear forces was scattered between 0.5 and 11 s^{-1} shwoing a left listed distribution with lower values when compared to the maternal ones.

Since the statistical behaviour of the Pearson's correlation coefficient value when analyzing the maternal and foetal erythrocyte aggregation under low shear forces did not differ much from that of the erythrocyte aggregation at stasis, we did not expect a much different scatter diagram. The scatter diagram of the values of erythrocyte aggregation under low shear forces at both the maternal and foetal sides is also

stretched over a wide range of values reflecting the weak calculated value of Pearson's correlation coefficient (r = 0.055) which is almost the same finding as with erythrocyte aggregation at stasis.

A completely different graphical pattern existed when analysing the correlation of maternal and foetal plasma viscosity, which is shown in Figure 6.

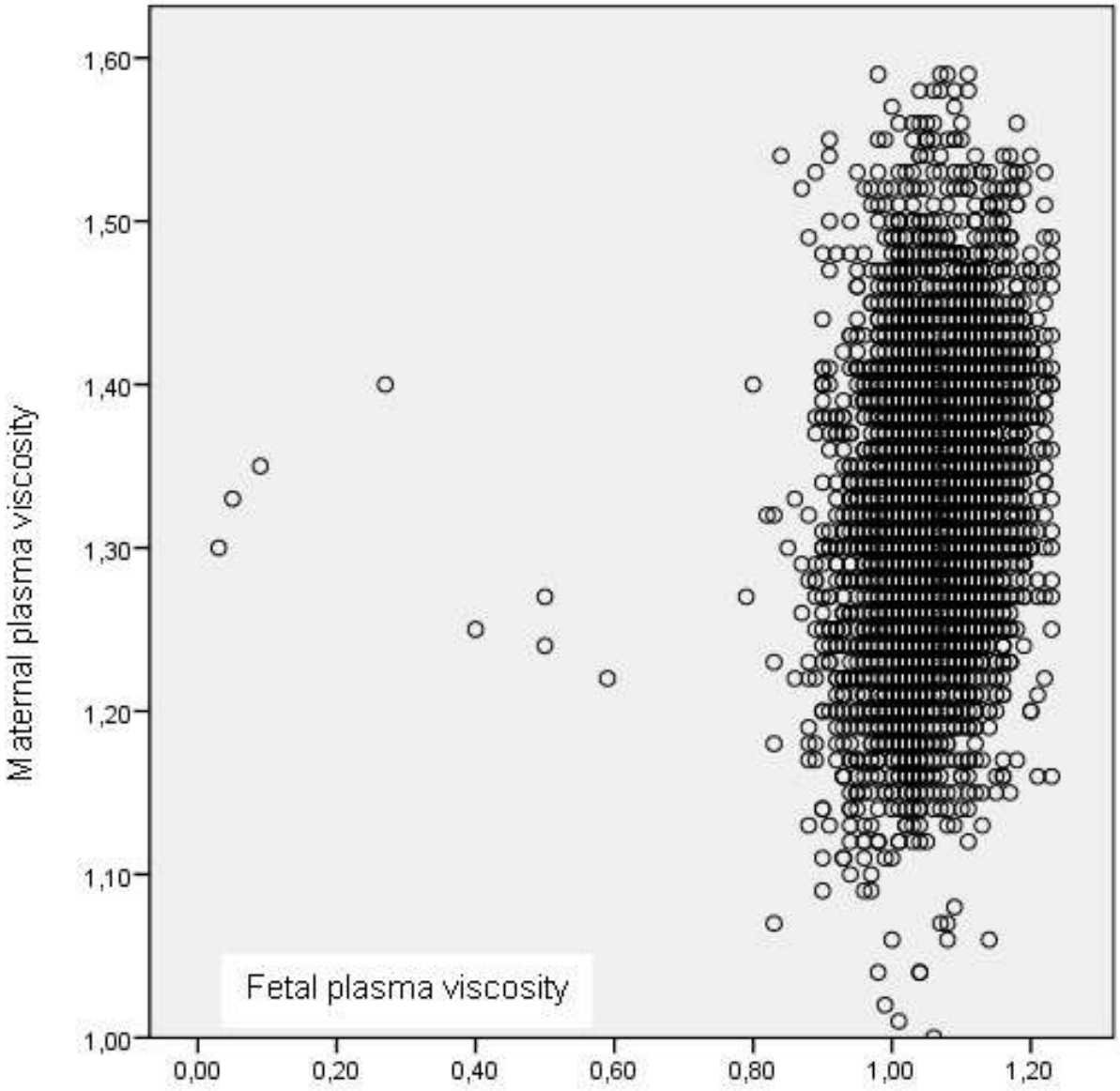

Figure 6. Scatter diagram correlating foetal to maternal plasma viscosity. One can note in this figure that 50% of the maternal values are scattered between 1.25 and 1.38 mPa s with a bell shaped distribution curve, on the other hand, 50% of the foetal plasma viscosity values are scattered between 0.55 and 1.13 mPa s, with obviously lower values than the maternal ones.

The scatter diagram representing the maternal and foetal plasma viscosity values shows a dense concentration of values over a small range, reflecting the high

calculated Pearson's correlation coefficient (r = 0.2) and hence the strong correlation noted ($p < 0.0001$).

Foetal rheological parameter variations in relation to advancing gestational age

When stratifying the newborns included in this study according to the gestational age at delivery, we found a strong positive correlation with high statistical significance between increasing foetal plasma viscosity and increasing gestational age as demonstrated by the corresponding Pearson's correlation coefficient value ($r = 0.197$; $p < 0.001$) (Figure 7). However, studying the maternal plasma viscosity in relation to gestational age did not show a statistically significant correlation, reflecting a steady maternal plasma viscosity regardless of the gestational age (N = 4,798, Pearson's correlation coefficient = 0.019; $p = 0.053$). In figure 7 a moderate but steady increase in the mean value of neonatal plasma viscosity can be noted starting the 27^{th} week of gestation (i.e. the gestational age at which we started including neonates in our analysis) that stretches and continues even to post term neonates (i.e. born after completed 40 weeks of gestation).

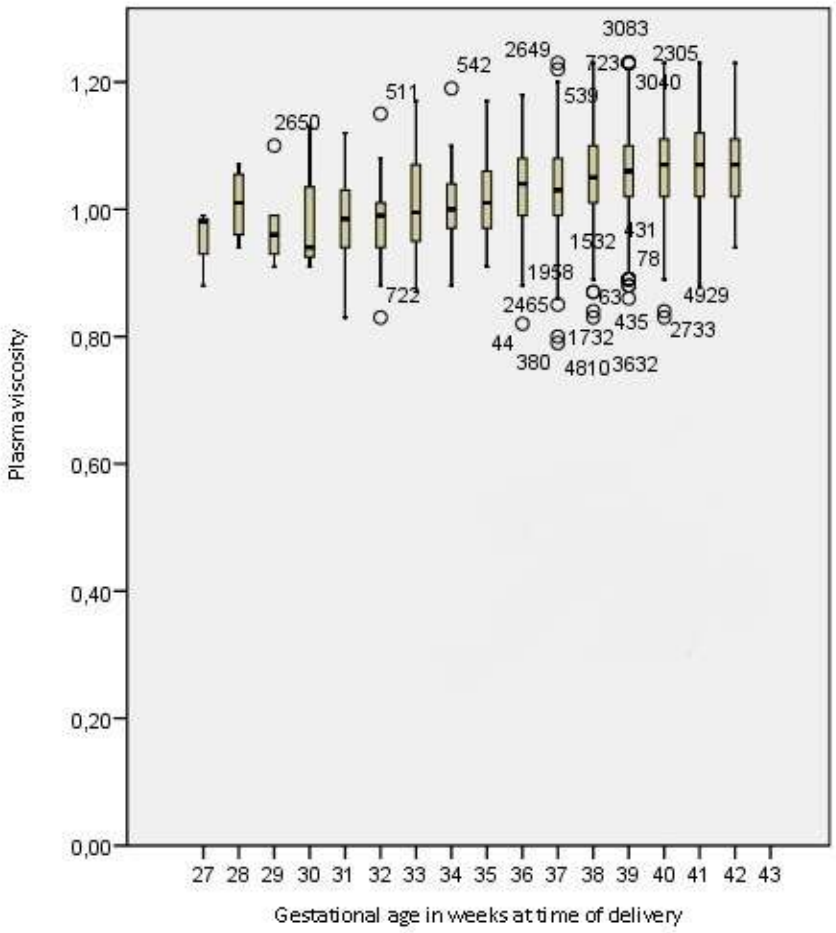

Figure 7: A box plot showing the plasma viscosity values in neonates according to the gestational age at birth, which lies between the 27th and the 43rd weeks of gestation.

When studying erythrocyte aggregation at stasis for the same group of neonates no statistically significant correlation could be found (N= 4,782, Pearson's correlation coefficient= -0.009, p = 0.534) (Figure 8) while foetal erythrocyte aggregation under low shear forces showed a weak but statistically significant negative correlation to the duration of gestation (N= 4803, Pearson's correlation coefficient = -0.031, p = 0.032) (Figure 9).

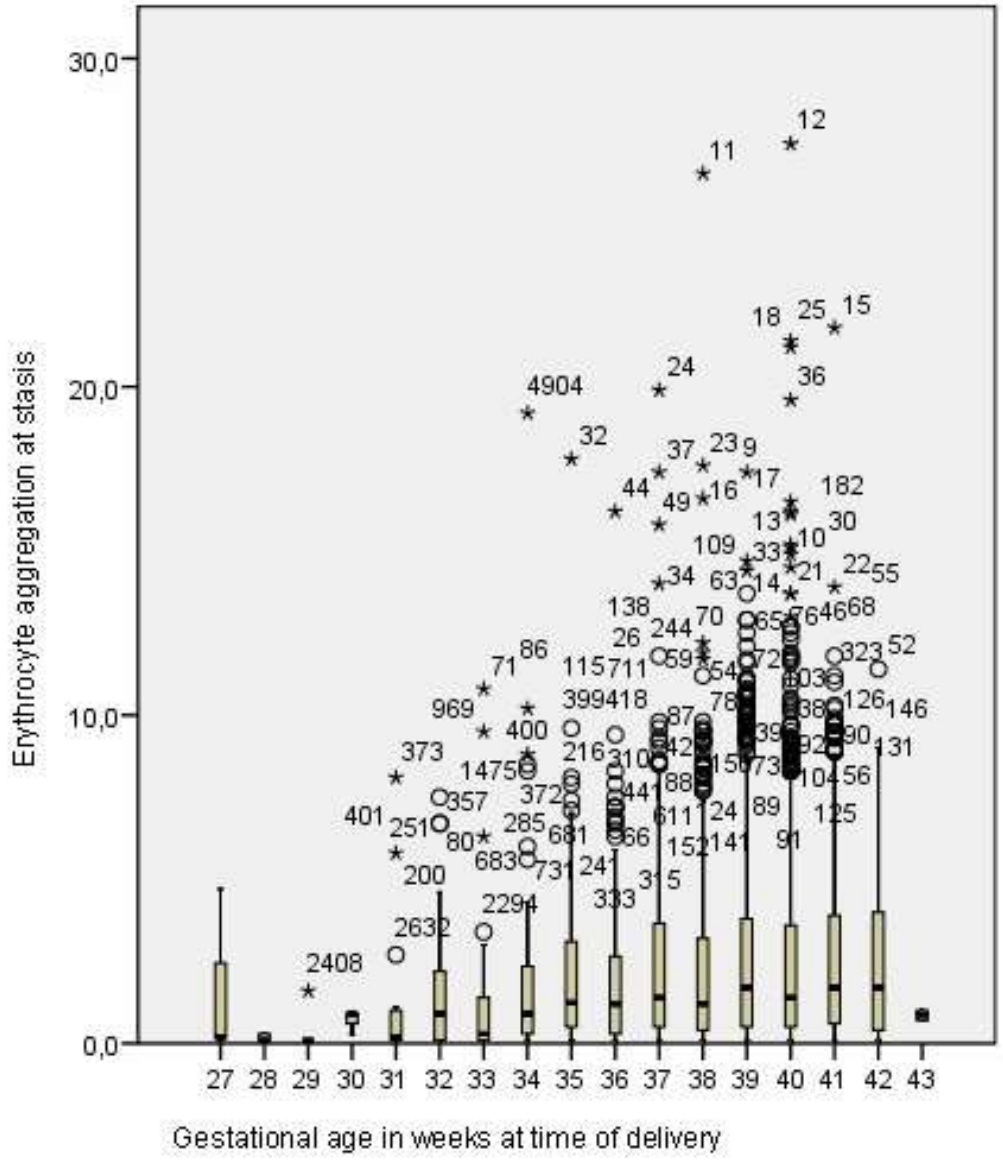

Figure 8 A box plot showing the erythrocyte aggregation values at stasis in neonates stratified according to the gestational age at birth, starting at the 27th week of gestation till the 43rd week of gestation.

In this Figure 8, the means of the values of neonatal erythrocyte aggregation at stasis did not shift almost at all with advancing gestational age at delivery reflecting the statistically non significant correlation observed.

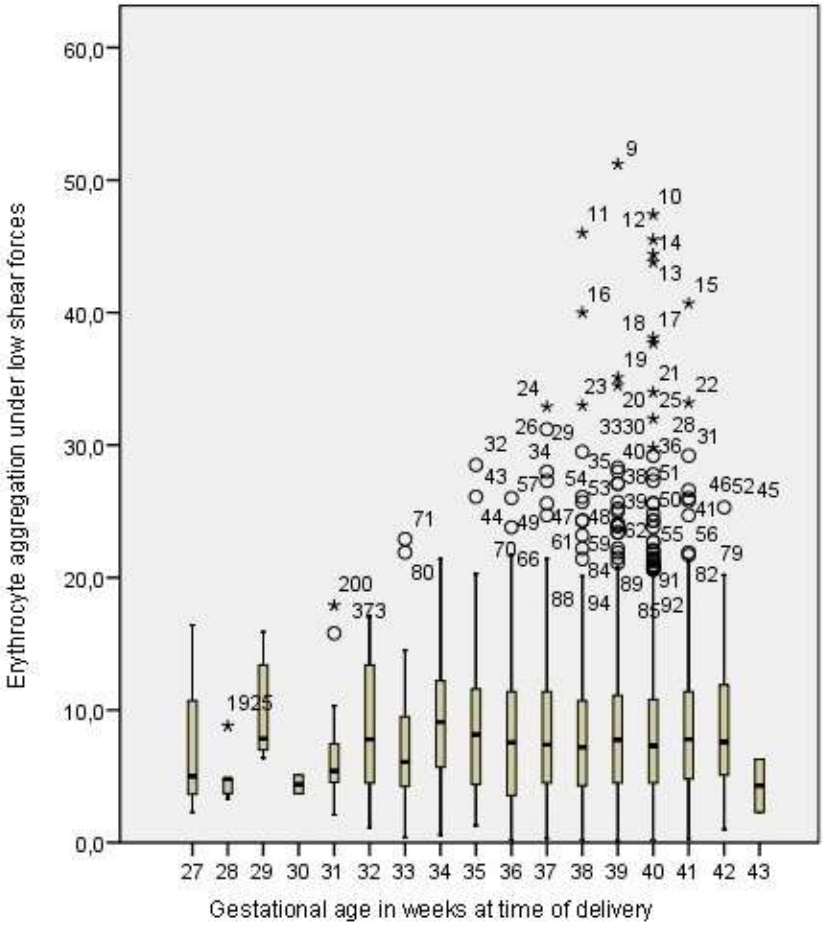

Figure 9 A box plot showing the erythrocyte aggregation values under low shear forces in neonates stratified according to the gestational age at birth, starting at the 27th week of gestation till the 43rd week of gestation.

In figure 9, the means of the values of the neonatal erythrocyte aggregation under low shear forces show a generally slight but steady decrease when correlated to gestational age at delivery. This decrease even extends to post term neonates.

Correlation of foetal rheological parameters under certain clinical circumstances

In the next step we studied the changes in rheological parameters of the newborns under the following circumstances.

Foetal blood rheology and maternal smoking

In our group of 4,985 patients we could gather data from 4940 pregnant from which 698 women were smokers (14%). Analysing the changes in foetal rheological parameters in cases of smoking compared to non-smoking mothers, we found statistically significant changes in all the examined foetal rheological and haematological parameters (table 4). We found statistically significant elevated mean values in the smoking group concerning the foetal hemoglobin ($p<0.0001^*$), the foetal hematocrit ($p<0.0001^*$), and the foetal plasma viscosity ($p = 0.049^*$). On the other hand, statistically significant lower values of the means of foetal erythrocyte aggregation both at stasis and under low shear forces for those neonates born to smoking mothers were confirmed in comparison to others born to non-smoking mothers ($p = 0.016^*$ and $p = 0.013^*$ respectively).

Table 4. Frequency distribution and analysis of variance (ANOVA) of the means of the rheological parameters of the newborns born to smoking and to non-smoking mothers.

		Hb	Hct	Pv	E0	E1
Smoking	**N**	698	697	692	692	685
	Mean	15.423	45.511	1.0613	2.159	7.835
	Range	5.4-20.8	10.3-61.2	0.8-1.23	0.1-21.2	0.2-32.0
	SD	1.8411	5.5057	0.06760	2.4499	4.7738
Non Smoking	**N**	4242[a]	4242[b]	4190[c]	4201[d]	4178[e]
	Mean	15.067	44.305	1.0554	2.428	8.364
	Range	3.3-22.5	5.6-66.2	0.03-1.23	0.1-27.4	0.1-51.2
	SD	1.8164	5.4975	0.07448	2.7598	5.2229
P-value		**<0.0001***	**<0.0001***	**0.049***	**0.016***	**0.013***

a 42 missing values, b 43 missing values, c 103 missing values, d 92 missing values and e 122 missing values. *is a statistically significant p value ($p < 0.05$). Hb = haemoglobin, Hct = haematocrit, Pv = plasma viscosity, E0 = erythrocyte aggregation at stasis, E1 = erythrocyte aggregation under low shear forces.

Foetal blood rheology and maternal Corticosteroid prophylaxis during pregnancy

We got almost identical results to those of smoking pregnant women, when looking for variations in the means of the values of the rheological and haematological parameters between pregnant women receiving corticosteroid prophylaxis during pregnancy and those who did not. The only exception was the foetal erythrocyte aggregation under low shear forces, which did not show statistically significant variation between the two subgroups (table 5). We found statistically significant lower values in the corticosteroid prophylaxis group comparing the means of the values of the foetal hemoglobin ($p<0.0001$*), the foetal hematocrit ($p<0.0001$*), the foetal

plasma viscosity (p<0.0001*) and the foetal erythrocyte aggregation at stasis (p = 0.007*).

Table 5: Frequency distribution and analysis of variance (ANOVA) of the means of the rheological parameters of the newborns born to mothers who received corticosteroid prophylaxis and those who did not.

		Hb	Hct	Pv	E0	E1
Corticosteroid prophylaxis	**N**	216	216	212	213	209
	Mean	14.446	42.372	1.0276	1.870	8.182
	Range	7.1-18.6	20.9-54.7	0.83-1.20	0.1-14.4	0.8-28.3
	SD	1.9446	5.7026	0.06846	2.2365	4.9635
Without Corticosteroid prophylaxis	**N**	4706[a]	4705[b]	4652[c]	4663[d]	4637[e]
	Mean	15.149	44.573	1.0577	2.418	8.304
	Range	3.3-22.5	5.6-66.2	0.03-1.23	0.1-27.4	0.1-51.2
	SD	1.8135	5.4895	0.07359	2.7380	5.1745
P-value		**<0.0001***	**<0.0001***	**<0.0001***	**0.007***	0.116

a 49 missing values, b 50 missing values, c 107 missing values, d 96 missing values and e 126 missing values. *is a statistically significant p value ($p < 0.05$). Hb = haemoglobin, hematocrit = haematocrit, pv = plasma viscosity, e0 = erythrocyte aggregation at stasis, e1 = erythrocyte aggregation under low shear forces.

Moreover, we analyzed our cohort of exclusively preterm neonates for variance between the means of different rheological parameters in those neonates whose mothers received corticosteroid prophylaxis and those who did not, and no statistically significant difference was found between both groups (table 6).

Table 6. ANOVA test analysing the variation of the means of the different foetal rheological parameters in the preterm group whose mothers received corticosteroid prophylaxis during pregnancy and those who did not.

		Hb	Hct	Pv	E0	E1
Corticosteroid prophylaxis	**N**	216	216	212	213	209
	Mean	14.446	42.372	1.0276	1.870	8.182
	Range	7.1-18.6	20.9-54.7	0.83-1.20	0.1-14.4	0.8-28.3
	Sd	1.9446	5.7026	0.06846	2.2365	4.9635
Without Corticosteroid prophylaxis	**N**	321	321	318	317	310
	Mean	14.731	43.369	1.0218	2.038	8.064
	Range	5.4-20.1	9.0-60.1	0.50-1.19	0.1-19.2	0.2-30.0
	Sd	2.2118	7.0709	0.07213	2.8352	5.1694
P-value		0.125	0.084	0.349	0.470	0.796

*is a statistically significant p value ($p < 0.05$). Hb = haemoglobin, Hct = haematocrit, Pv = plasma viscosity, E0 = erythrocyte aggregation at stasis, E1 = erythrocyte aggregation under low shear forces.

Foetal blood rheology and maternal iron supplementation during pregnancy

The variations of rheological parameters between the neonates whose mothers received iron supplementation during pregnancy and those who did not, were statistically significant among all the studied parameters, except for the foetal plasma viscosity which was not (table 7). We found statistically significant lower levels in the iron supplementation group in the mean values of the foetal hemoglobin ($p<0.0001$*) and the mean values of the foetal hematocrit ($p<0.0001$*). We found statistically significant higher values in the iron supplementation group in the foetal erythrocyte aggregation at stasis ($p<0.0001$*) (Figure 10) and the foetal erythrocyte aggregation under low shear forces ($p<0.0001$*) (Figure 11). The mean values of the foetal plasma viscosity were lower in the iron supplementation group, but the change was not statistically significant ($p = 0.068$).

Table 7. Frequency distribution and analysis of variance (ANOVA) of the means of the rheological parameters of the newborns born to mothers who received iron supplementation and those who did not.

		Hb	Hct	Pv	E0	E1
Iron supplementation	**N**	406	406	392	403	403
	Mean	14.803	43.520	1.0497	3.326	9.755
	Range	5.4-19.8	10.3-58.2	0.79-1.22	0.1-19.9	0.3-34.5
	SD	1.7886	5.3847	0.0704	3.2329	5.6759
Without Iron supplementation	**N**	4534[a]	4533[b]	4490[c]	4490[d]	4460[e]
	Mean	15.146	44.561	1.0568	2.306	8.157
	Range	3.3-22.5	5.6-66.2	0.03-1.23	0.1-27.4	0.1-51.2
	SD	1.8246	5.5181	0.07381	2.6530	5.0962
P-value		**<0.0001***	**<0.0001***	0.068	**<0.0001***	**<0.0001***

a 45 missing values, b 46 missing values, c 103 missing values, d 92 missing values and e 122 missing values. *is a statistically significant p value ($p < 0.05$). Hb = haemoglobin, Hct = haematocrit, Pv = plasma viscosity, E0 = erythrocyte aggregation at stasis, E1 = erythrocyte aggregation under low shear forces.

We graphically represented our data concerning erythrocyte aggregation at stasis in Figure 10 where the median of the values of neonatal erythrocyte aggregation at stasis was statistically significant higher in the group whose mothers received iron supplementation during pregnancy in comparison to those who did not.

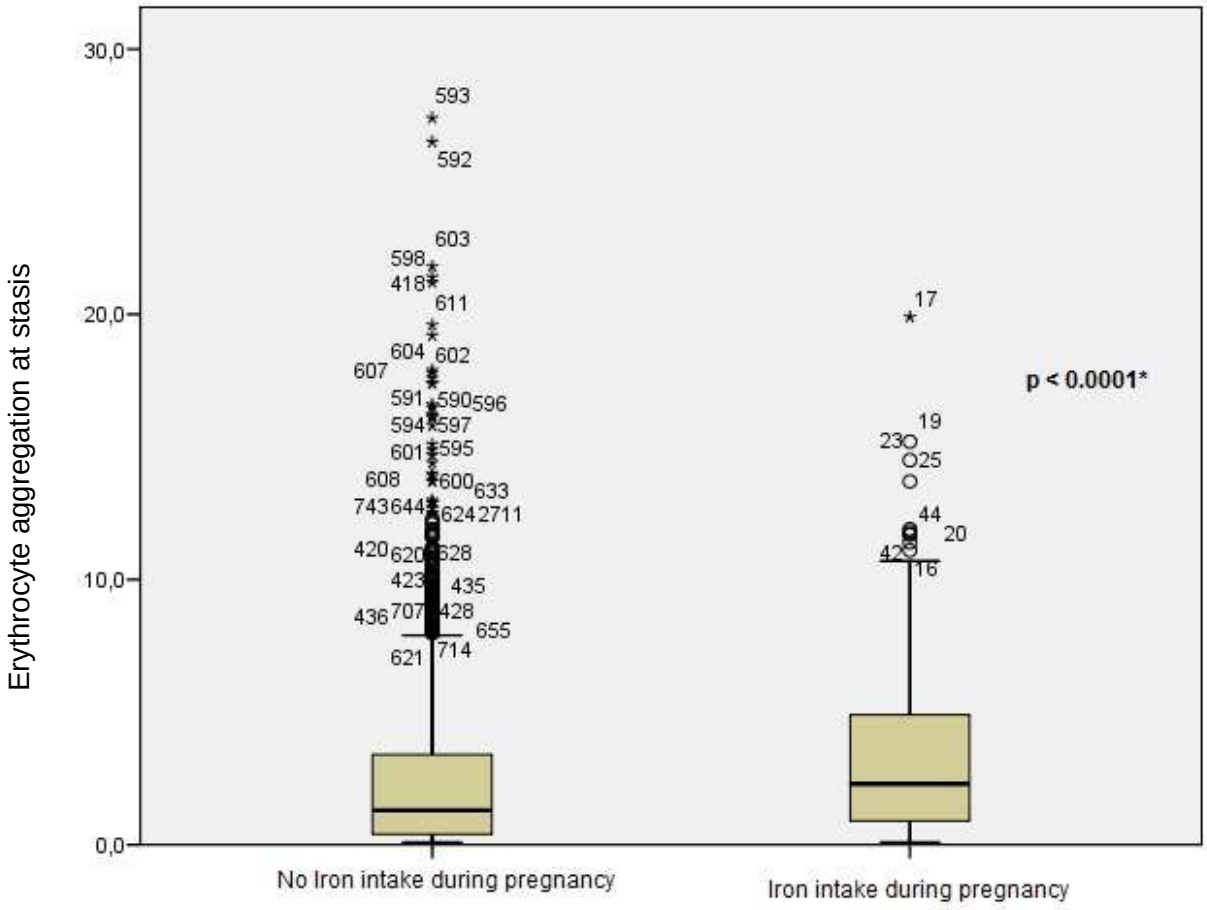

Figure 10. Box plot showing the erythrocyte aggregation at stasis among the group of neonates whose mothers received iron supplementation during pregnancy and the group who did not. (Median, 25% and 7% quartiles, and outliers).

As shown in Figure 11 the median of the values of neonatal erythrocyte aggregation under low shear forces was statistically significant higher in the group whose mothers received iron supplementation during pregnancy in comparison to those who did not

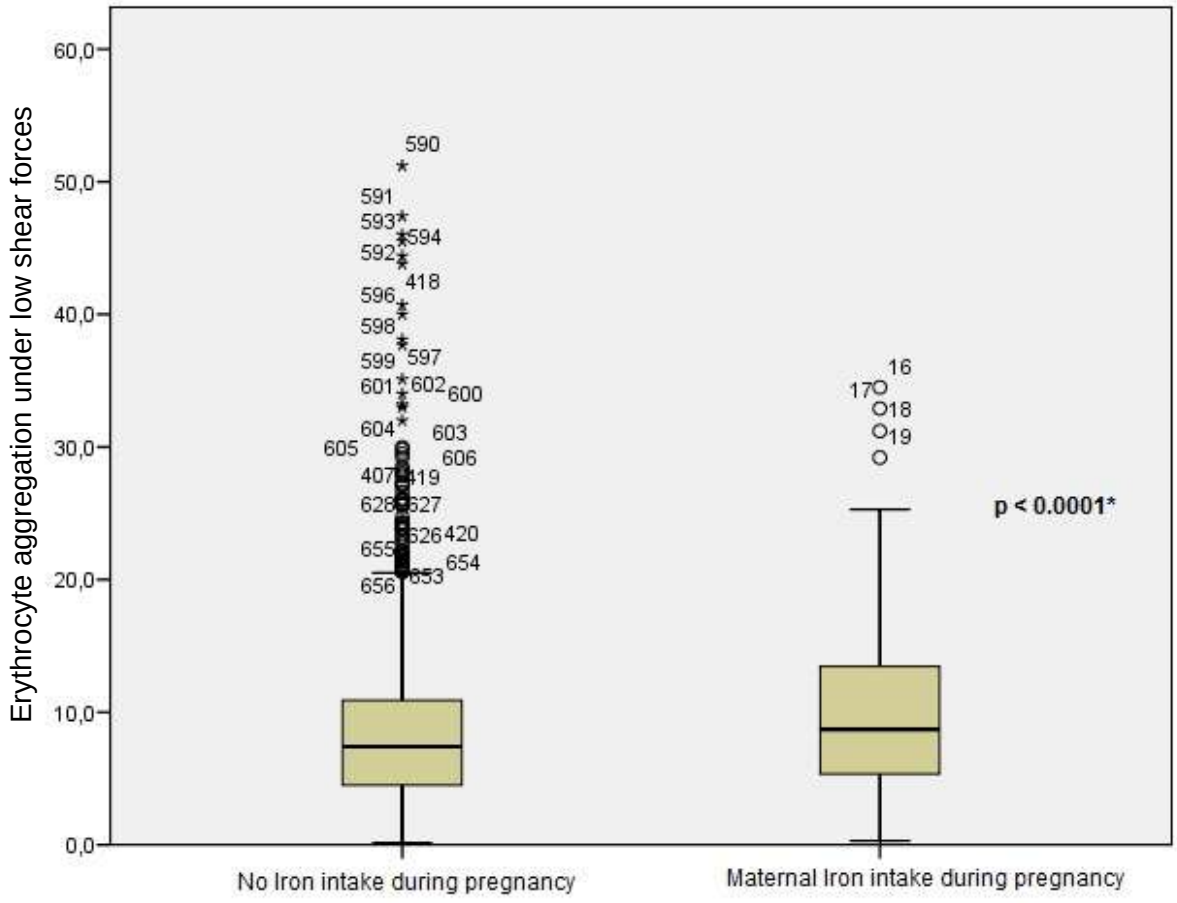

Figure 11. Box plot showing the erythrocyte aggregation under low shear forces among the group of neonates whose mothers received iron supplementation during pregnancy and the group who did not. (Median, 25% and 75% quartiles, and outliers).

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Diskussion (Discussion)

This retrospective cross sectional study, included data from 4,985 healthy women giving birth at the labour and delivery unit of the Women's Hospital of City Hospital of Rüsselsheim, as well as their newborns. The data was stored by the physicians attending the deliveries and providing medical care to the pregnant women, then was digitalized, tabulated and analyzed by the candidate to finish this work. This huge number of included subjects gives the results a high statistical power, but on the other hand, the retrospective design of the study and the long time period between the registration of data and its digitalization and statistical analysis, both have a negative impact on the significance of the results. This has to be put in consideration during the critical appraisal of this work. In the same time, our knowledge concerning foetal and maternal blood rheology, maternal smoking during pregnancy, corticosteroid prophylaxis and maternal iron intake during pregnancy did not significantly change between the time point of collecting the data and its analysis. We hope through this work to add valuable information to the actual scientific knowledge concerning the studied areas.

Blood plasma is a heterogeneous fluid that follows Newtonian laws of flow of fluids, whose viscosity depends on the concentration of different protein particles, such as albumin, lipoproteins and immunglobulins and in particular, fibrinogen that plays a predominant role in determining plasma viscosity (1). This may also explain the obviously strong positive and highly significant correlation ($r = 0.197$; $p < 0.001$) between foetal plasma viscosity and duration of gestation, where the newborns usually show ever maturing protein synthesis by the liver with increasing levels of plasma proteins e.g. fibrinogen when comparing term to preterm infants (65). The plasma viscosity in a normal healthy neonate at term was found to be between 0.98 and 1.132 mPa s ($m = 1.06$, $SD = 0.072$ mPa s) (45) indirectly reflecting normal liver function regarding protein and coagulation factor production. Thus from the published data showing significant increase in liver production of coagulation factors and plasma proteins at term compared to preterm neonates (65) and from our observation that neonatal plasma viscosity is highly significantly positive correlated to advancing gestational age at delivery, with no significant correlation between maternal plasma viscosity and increasing gestational age, it is very likely that neonatal plasma viscosity at birth may be a biological marker of foetal liver function maturity. Since all healthy neonates in the current study had no signs of any disease,

additional laboratory assessment, such as C-reactive protein (CRP) were not routinely performed. Thus, although unlikely, we cannot rule out the presence of inflammatory or immunologic responses to certain disease that might have influenced plasma viscosity. This has to be further validated and the precise values of plasma viscosity for the corresponding weeks of gestation should also be further clarified. What remains to be explained is the significant weak inverse proportion between erythrocyte aggregation under low shear forces and the gestational age; this contradicts actually our knowledge about erythrocyte aggregation and liver function in newborn infants. Based on this knowledge, where erythrocyte aggregation correlates positively to plasma concentration of fibrinogen (66), we expected a positive correlation instead of the negative correlation we found in our cohort. The observation concerning erythrocyte aggregation at stasis is even more difficult to clarify, where a very weak negative non-significant correlation was noted. Foetal erythrocytes, as mentioned before, are somewhat different compared to that in adults, where foetal erythrocyte deformability is higher when compared to that of pregnant women (44,46) and because of that, fibrinogen induced interaction between foetal erythrocyte may be reduced. However, we could not find a clear explanation for these two observations.

Another interesting observation was the mutual positive significant correlation between single maternal and foetal rheological parameters, except foetal erythrocyte aggregation at stasis which showed an inverse proportional weak relationship to maternal plasma viscosity which was also of low statistic significance. Foetal erythrocyte aggregation under low shear forces was not at all significantly correlated to maternal plasma viscosity, and maternal erythrocyte aggregation under low shear forces showed a very weak negative and non-significant correlation to foetal plasma viscosity. However, the statistic significance of some observations was very high as it was between maternal erythrocyte aggregation at stasis and foetal erythrocyte aggregation both at stasis and under low shear forces. This high statistic significance was, as a matter of fact, due to the large sample size included in the statistical analysis and not actually reflecting a specially strong correlation. Interestingly, there was a strong and statistically significant correlation as well between foetal and maternal plasma viscosity ($r = 0.2$), Trying to analyse our findings, the maternal-foetal transport may play a crucial role in determining the foetal physiological milieu, a function that is solely controlled by the placenta. The placenta is a multi-function organ, where transport between maternal and foetal circulations is one of those

functions. Transport across the placenta is a complex non-homogeneous process. In classical teaching it was long believed that mainly water and electrolytes could easily pass across the placental barrier, with some proteins like IgG as exceptions, while the transfer of foetal cells across the placental membrane to maternal circulation was considered as an absolute rarity (19). This however is a very controversial issue, and many reports have changed this view, pointing out regular exchange of proteins and cells across the placenta (67). We tried to explain our observations according to the best available level of knowledge. The very strong and highly significant positive correlation between maternal and neonatal plasma viscosity could be explained through balancing the water content of maternal and foetal plasma through placental aquaporines which regulate water transport according to osmotic pressure difference across the placental barrier (68-70).

What we could not explain was however the mutual inverse correlation between plasma viscosity and erythrocyte aggregation at stasis on both sides. The correlation is anyway negative, weak and of weak statistic significance, but still, this finding contradicts published data, because erythrocyte aggregation is also mostly influenced by plasma protein concentration (2). Moreover, the lack of significant correlation between neonatal erythrocyte aggregation under low shear forces and maternal plasma viscosity needs to be further investigated.

Increasing foetal plasma viscosity when put together with the already high foetal hematocrit means that foetal whole blood viscosity would probably also increase with increasing gestational age. This increase in whole blood viscosity could be sonographically detected using Doppler flow resistance index in the umbilical arteries as stated by Giles et al. who demonstrated a correlation between increased Doppler flow resistance indices in the umbilical artery and increased whole blood viscosity accompanying increased foetal blood hematocrit (41). In adverse outcome pregnancies, for example preeclampsia or IUGR, maternal erythrocyte aggregation and maternal hematocrit are significantly higher than in normal pregnancy. Although the plasma viscosity was not significantly different in preeclampsia when compared to normal pregnancy, it was however even lower in IUGR pregnancies than in normal pregnancies (23). This significant increase in hematocrit and erythrocyte aggregation will of course have an impact on whole blood viscosity, which can also contribute to the increasing maternal Doppler indices in such cases.

Neonatal and maternal haematological parameters showed strong correlations to each other which were also highly statistically significant. Maternal and foetal

haemoglobin values were highly correlated to each other and to hematocrit values too. Our Pubmed search did not return meaningful results concerning this issue. Most of the authors related maternal haemoglobin and hematocrit to pregnancy outcome and not to foetal haematological outcomes. Only one report found a significant correlation between maternal iron deficiency anemia and neonatal low levels of serum ferritin. This report however, did not examine foetal haemoglobin or hematocrit levels. Moreover, it could not find a statistically significant correlation between maternal iron deficiency anemia and neonatal serum iron nor neonatal total iron binding capacity (71). Gambling et al. used an animal model trying to understand the placental iron transport and its regulating factors, they found out that the fetus takes the highest priority when it comes to maternal iron deficiency, then maternal hemotocrit comes next and finally maternal iron stores, which are the last to be replenished when iron is supplemented as a result to maternal iron deficiency anemia. They gave clue that the fetus can control to a considerable extent the iron transport across the placenta through regulating the density of the transferring receptors located on the microvillar membrane of the placenta (72,73). This assumption is not supported by our finding that foetal haemoglobin takes the same trend as maternal haemoglobin, and that was even clear when comparing foetal haemoglobin levels in neonates born to mothers receiving iron supplementation to mothers who did not receive any iron supplementation. The mean foetal haemoglobin was higher in the group born to mothers that did not receive any supplementation most probably because they did not suffer any anemia, a finding that even emphasises this strong correlation between maternal and foetal haemoglobin and hematocrit levels. The correlation between maternal and foetal haemoglobin and hemtocrit remains however unclear and needs thus to be further investigated .

The respiratory distress syndrome in premature newborns is one of the major causes of neonatal mortality worldwide. It is caused by developmental insufficiency of surfactant production and structural immaturity in the lungs (74) and the mortality and morbidity rates can be significantly reduced using steroid prophylaxis applied to the pregnant woman in a timely fashion before the delivery, if it is possible to achieve a steroid prophylaxis over 48 hours before delivery sets sails (61). Surfactant constitutes of complex molecules formed of lipids, proteins and glycoproteins clumped together and are produced in specialized lung cells, called Type II pneumocytes (74). A lot of research was performed on the benefits and the risks of steroid prophylaxis therapy both on the pregnant women and their newborns.

However, to date, no one studied the effect or the changes in the haemo-vascular milieu of the mothers and their newborns after steroid prophylaxis. We did a Pubmed literature search with the keywords corticosteroid prophylaxis and hemorheology, corticosteroid prophylaxis and plasma viscosity, corticosteroid prophylaxis and erythrocyte aggregation and corticosteroid prophylaxis and vascular changes in neonates and unfortunately the search returned no valuable results. However, we used the work of Finke (75) and Wiek (76) to explain these observations. Fink found in his cohort of giant cell arteritis patients a significant increase in plasma viscosity (75). The same finding was confirmed by Wiek who took a step further proving that corticosteroid intake significantly lowered the already existing high plasma viscosity values even to levels lower than controls (76). We applied this fact, that corticosteroids lower the plasma viscosity somehow, to our cohort in order to explain the significantly lower plasma viscosity as well as the other blood rheological parameters in neonates to mothers who received steroid prophylaxis. The pregnant women who received steroid prophylaxis would, according to the existing data, experience lowered plasma viscosity, due to fluid retention which is a known effect of corticosteroids, resulting in increasing the fluid part of the plasma and hence lowering its viscosity, where this would be subsequently reflected on their foetuses and newborns where we already observed a significant correlation between maternal and neonatal rheological parameters, and explained it. Another explanation of this observation can be also attributed to the immune suppressive effect of corticosteroids. Plasma viscosity does not depend only on Fibrinogen, which is though the most important determinant protein of plasma viscosity, it rather depends also on immunoglobulins and other inflammatory proteins whose production could be suppressed in the fetus under the effect of corticosteoids resulting in this decrease in plasma viscosity. As mentioned above, we could not find a thorough investigation concerning this point, thus our postulations will still remain as theoretical possible explanations until a trial investigates and validates these findings.

When we compared the blood rheology parameters of preterm newborns from mothers who received steroid prophylaxis to those preterm newborns whose mothers did not receive corticosteroids, we found no significant difference between the values of both groups, which was against our expectations. We assume accordingly that the significant difference between the group of newborns whose mothers received corticosteroids and the rest of the cohort whose mothers did not receive corticosteroid might actually be due to the effect of prematurity with immature liver

protein production in those neonates rather than the effect of corticosteroid intake. This point needs to be further scrutinised and explained.

Smoking is a health risk factor in general and particularly during pregnancy, where it is more prevalent in pathologic pregnancies; smoking during pregnancy is associated with low neonatal birth weight (77). The effect of smoking on maternal rheological parameters is an interesting issue that was previously investigated and the published report pointed out that smoking was associated with higher maternal haematocrit and lower maternal erythrocyte aggregation at stasis and under low shear forces (23). These findings go along with the rheological findings in non pregnant patients with cardiovascular diseases where smoking is associated with a significant increase in haemoglobin, haematocrit and plasma viscosity (78,79). The foetal haematological and rheological parameters in our cohort followed the same trend as it is in maternal blood. Smoking was associated with an increased foetal Hemoglobin, Hematocrit and plasma viscosity. Cigarette smoking alters the placental structure as early as the first trimester, so the fetus has to stimulate its own erythropoesis in order to increase the oxygen carrying capacity of blood to be capable of supplying the normal nutritional needs (80). This increase in red blood cell mass results in a further increase in whole blood viscosity leading to a vicious circle of decreasing flow and hypoxia (81). In the extensive capillary microcirculation of the placental villi, raised plasma viscosity and reduced erythrocyte deformability will lead to reduced blood flow. The reduced intra-villous perfusion combined with reduced blood flow in the maternal blood lacunae due to the effects of nicotine, lead to a substantial restriction in the foetal ability to grow (80). These published observations could also explain the increased neonatal haemoglobin and hematocrit in our cohort, but could not explain the increased plasma viscosity and decreased erythrocyte aggregation both at stasis and under low shear forces in neonates born to smoking mothers when compared to those born to non smoking mothers. Our literature search did not return any published data correlating smoking to increased maternal plasma viscosity in pregnancy, and moreover, no data investigating neonatal rheological parameters to smoking mothers. The only published data we found was concerned with rheological parameters in smoking pregnant women and did not find significant changes correlating smoking with plasma viscosity, the only significant difference was with hematocrit and erythrocyte aggregation (23). Our results conform however with these published results as regards the reported parameters. We could explain the changes in foetal rheological parameters by simply following the trend in maternal rheological

parameters, as already published (23) (i.e. higher hematocrit and lower erythrocyte aggregation both at stasis and under low shear forces), and as we already observed the significant trend of foetal hemorheological parameters to follow those of the mother. The observation that we could not explain was however the significant increase in plasma viscosity in neonates born to smoking mothers. We could not find a published explanation to this observation nor another report to confirm it.

In most developing countries, anaemia is a leading cause of adverse pregnancy outcome (82). Iron supplementation during pregnancy significantly enhances maternal iron status including, serum iron, transferrin saturation, serum ferritin in addition to haemoglobin and Mean Cell Volume (MCV) (83). Those, who received iron-supplementation due to anaemia, had significantly lower plasma viscosity which is probably due to a higher intra-vascular fluid volume rather than an insufficient erythropoiesis (23). The changes in foetal rheological parameters in our cohort, regarding iron supplementation, followed the corresponding maternal changes, except for plasma viscosity which was lower in the iron supplementation group but still not statistically significant. This significant change could however be explained by the observations of von Tempelhoff et al. (23) and through our own observation of the significant correlation between various maternal and foetal rheological parameters. The lower neonatal plasma viscosity could follow the lower maternal plasma viscosity, and the correlation between both maternal and neonatal plasma viscosities is already proved through our results. This applies to erythrocyte aggregation at stasis, which was significantly lower in neonates born to mothers receiving iron supplements in comparison to those who did not. What we could not find an explanation for, is the significant inverse relationship between maternal and neonatal erythrocyte aggregation under low shear forces. We did a literature search using the key words erythrocyte aggregation under low shear forces, iron supplementation in pregnancy, maternal and neonatal erythrocyte aggregation under low shear forces, but our search returned no valid results. This needs to be further investigated and validated.

From this study we were able to conclude the following:

- An increasing neonatal plasma viscosity that significantly correlates to the increasing gestational age probably reflects an increasing ability of the foetal liver in protein synthesis, thus allowing us to conclude that neonatal plasma

viscosity may be a reliable laboratory parameter reflecting the maturation of the foetal protein synthesis process.

- Foetal and maternal haemoglobin and hematocrit levels are correlated by a strong significant relationship, whose explanation is still unclear, thus an explanation to this observation should be sought.

- The effect of immature foetal liver protein production might have a higher impact on foetal plasma viscosity than the effect of corticosteroid prophylaxis. This observation needs to be further validated and explained.

- Smoking, iron supplementation during pregnancy and corticosteroid prophylaxis during pregnancy are all common clinical situations that significantly affect neonatal rheological parameters and consequently its microcirculation. Further studies are needed to confirm our findings and to clarify the reasons behind these findings and explain them.

Zusammenfassung

Dies ist eine retrospektive Beobachtungsstudie, die die Korrelation zwischen hämorheologischen und hämatologischen Parametern bei Müttern und ihren Neugeborenen zum Zeitpunkt der Entbindung untersuchte. Wir rekrutierten gesunde Normalschwangerschaften und untersuchten zudem Subpopulationen, e.g. Mütter die während der Schwangerschaft rauchten, eine Eisensubstitution erhielten oder eine Kortikosteroide erhielten zur RDS-Prophylaxe bei drohendem Frühgeburt.

Lediglich die Messergebnisse der foetalen Plasmaviskosität zeigten im Gegensatz zu den mütterlichen Resultaten einen statistisch hoch signifikanten Anstieg mit zunehmender Tragzeit. Bemerkenswerterweise bestand auch eine hohe positive Korrelation zwischen foetaler und mütterlicher Plasmaviskosität, währenddessen nur eine moderate Korrelation für die foetale und mütterliche Erythrozytenaggregation - sowohl in *stase* als auch unter *low shear* Bedingungen – ermittelt werden konnte. Die Konstellation dieser beobachteten Korrelationen ließe sich damit erklären, dass mütterliche Plasmaproteine aktiv oder passiv diaplazentar zum Feten gelangen und damit auch Einfluss auf die foetale Plasmaviskosität – letztlich auch auf das onkotische Gleichgewicht - nehmen. Weitere Studien hierzu sind erforderlich, in den eine Quantifizierung und Qualifizierung unserer Annahme zu validieren. Die Gestationsalter abhängige kontinuierliche Zunahme der foetalen Plasmaviskosität ab der 27. bis 42 Schwangerschaftswoche ist vermutlich auch als indirekter Hinweis der fortschreitenden Organreifung und - im Speziellen - der Proteinsynthese Leistung der foetalen Leber zu werten. Damit käme der Plasmaviskosität in der Normalschwangerschaft möglicherweise als Labor-Marker für die Beurteilung der foetalen Leber Reife eine Bedeutung zu.

Die maternale Kortikosteroid-Prophylaxe zur RDS Prophylaxe bei drohender Frühgeburtlichkeit hatte indes keine statistisch relevanten Auswirkungen auf die foetale und maternale Blutrheologie. Obgleich Feten nach RDS Prophylaxe gegenüber Unbehandelten statistisch signifikant niedrigere Plasmaviskositäten bei Geburt aufwiesen, konnte Tragzeitbereinigt kein Unterschied nachgewiesen werden. Ein Einfluss auf die foetale und maternale Blutrheologie und insbesondere Plasmaviskosität durch eine mögliche Kortikosteroid induzierte Synthesehemmung immunkompetenter Proteine einerseits bzw. eine Stimulation der foetalen Proteinsynthese in der Lunge oder Leber andererseits ließ sich in dieser Studie nicht belegen. Interessanterweise führte Rauchen in der Schwangerschaft zu statistisch

signifikant höheren Erythrozytenaggregationen und Plasmaviskositäten bei gleichzeitig deutlich höheren Hämoglobin und Hämatokrit Werten als Zeichen einer relativen Hyperviskosität bei den betroffenen Feten. Diese blutrheologischen und hämatologischen Veränderungen auf foetaler Seite korrelieren damit eng mit denen auf mütterlicher Seite in der Literatur beschrieben.

Inwieweit die blutrheologischen Eigenschaften durch diaplazentare Mechanismen oder relativer Hypoxie im Zuge einer häufig dopplersonographisch nachvollziehbaren plazentaren Flussminderung zustande kommt, muss in zukünftigen Studien geklärt werden. Die Eisensubstitution in der Schwangerschaft führt bei Mutter und Feten zu statistisch signifikant höheren Hämoglobin- und Hämatokritwerten. Diese Veränderungen gingen rheologischer Seits auch mit einer statistisch signifikanten Steigerung der Erythrozytenaggregation ohne nachweisbaren Einfluss auf die Plasmaviskosität. Da die Messung der Erythrozytenaggregation Hämatokrit bereingt erfolgt geht die gesteigerte foetale Erythropoese möglicherweise auch mit einer veränderten Funktionalität und Bindungsaffinität der Erythrozyten einher.

Als wichtigste Schlussfolgerungen der vorliegenden Studie ergeben sich:

- Eine tragzeitabhängige kontinuierliche Zunahme der foetalen Plasmaviskosität bei Entbindung korreliert im hohen Maße mit der maternalen Plasmaviskosität und ist möglicherweise Ausdruck der reifenden foetalen Lebersyntheseleistung.
- Ein Einfluss der Korticosteroid-haltigen RDS Prophylaxe auf die foetale Blutrheologie konnte nicht nachgewiesen werden.
- Rauchen während der Schwangerschaft bedingt die Ausbildung einer relativen Hyperviskosität der betroffenen Feten
- Die Eisensubstituition in der Schwangerschaft geht auch auf foetaler Seite mit höheren Hämoglobin und Hämatokrit Werten und einer erhöhten Neigung der Erythrozyten zu aggregieren.

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Arabisch: Muttersprache

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Mar 2003 bis Dez. 2003	▪ **Allgemeinarzt** Alexandria Gesundheitsbehörde, Ministerium für Gesundheit und Bevölkerung, Ägypten
Mar 2002 bis Feb 2003	▪ **Praktisches Jahr** Alexandria Uniklinik, Alexandria Universität, Ägypten

ZUSÄTZLICHE BERUFLICHE ERFAHRUNGEN

Oktober 2012 –	▪ **Sub-Investigator.** TROCADERO Studie. Klinikum Aschaffenburg Stelle. OPTUM insight™.
September 2012 -	▪ **Koordinator.** Gynäkologisches Krebszentrum. Klinikum Aschaffenburg.
Apr 2008 bis Okt	▪ **Daten-Koordinator.** ‚Misoprostol for Postabortion Care' El Shatby

2008 Uniklinik Stelle. Gynuity Health Projects Inc.

Aug 1999
- Austausch Student. Augenheilkunde Abteilung, VFN Uniklinikum, Prag, Tschechische Republik

WORKSHOPS

- **‚AGE Fortgeschrittenenkurs MIC II Gynäkologische Endoskopie'** 26. – 27.02.2013, Augusta-Kranken-Anstalt Bochum, Frauenklinik, Bochum. (ein AGE zertifiziertes Training-Zentrum).
- **20. Jahrestreffen der AGO Studiengruppe.** 30.11.2012, Empire Riverside Hotel, Hamburg.
- **Hochschuldidaktische Fortbildung ‚Praxisworkshop Präsentation'.** 29.11.2012, medizinische Fakultät Würzburg, Würzburg.
- **Hochschuldidaktische Fortbildung ‚Multiple Choice- Prüfungen für Mediziner'.** 15.11.2012, medizinische Fakultät Würzburg, Würzburg.
- **Hochschuldidaktische Fortbildung ‚Mündliches Staatsexamen für Mediziner'.** 14.11.2012, medizinische Fakultät Würzburg, Würzburg.
- **Hochschuldidaktische Fortbildung 'Training kommunikativer Fertigkeiten unter Einsatz von Schauspielpatienten'.** 18.10.2012, medizinische Fakultät Würzburg, Würzburg.
- **XX FIGO World Congress of Gynecology and Obstetrics.** 07.-12.10.2012, Fiera di Roma, Rom, Italien.
- **6 Rhein-Main gynäkologische Onkologie Symposium,** 22.09.2012, deutsche nationale Bibliothek, Frankfurt.
- **'GCP-Schulung, Studienupdate'** 16.06.2012, Johannes Wesling Klinikum, Minden.
- **3rd International Video Workshop on Radical Surgery in Gynaecological Oncology.** 26.-28.04.2012, Prag , Tschechische Republik.
- **Mammasonografie Aufbaukurs.** 20.-21.04.2012. städtisches Klinikum Lüneburg.
- **Mammasonografie Grundkurs.** 03.-04.02.2012. städtisches Klinikum Lüneburg.
- **5 Rhein-Mainz gynäkologische Onkologie Symposium, Offenbach, 17.09.2011.**
- **17th International Meeting of the European Society of Gynecological Oncology. Mailand, Italien, 11.-14. September, 2011.**
- **13th Biennial Meeting of the International Gynecologic Cancer Society. Prag, Tschechische Republik, 23. – 26. Oktober, 2010.**
- **8.Regionaltreffen des Studienleitzentrums der AGO Ovarialkarzinom: Innovationen in der Therapie des Ovarialkarzinoms. 29.09.2010.**
- **Veranstaltung Urogyn 2: Diagnostik und conservative Therapie. 17.03.2010.**
- **Veranstaltung Urogyn 1: Die Chirurgische Anatomie des weiblichen Beckens. 17.02. 2010.**
- **7.Regionaltreffen des Studienleitzentrums der AGO Ovarialkarzinom: Innovationen in der Therapie des Ovarialkarzinoms. 18.11.2009**
- **7th World Congress of Foetal Medicine' Sorrento, Italien, 22.–26. Juni 2008.**
- **Workshop zum Thema Scan-foetalen Anomalien. El Shatby Uniklinikum, 22.- 23. April 2008.**

- 4th Konferenz der Ägyptischen Menopausegesellschaft. Alexandria, Ägypten, 12.- 14. März 2008.
- Statistische Prozesskontrolle für das Gesundheitswesen Qualitätsmanagement. Medizintechnisches Zentrum, Alexandria Universität, Ägypten. 25.- 26. Juli 2007.
- Forschungs-Methodik. Alexandria Universität, Ägypten. 14.- 16. April 2007.
- Kommunikationsfähigkeiten. Alexandria Universität. 10.- 12. April 2007.
- **Klinischer Kurs für gynäkologische Endoskopie. Alexandria Endoscopy Association (ALEXEA) in zusammenarbeit mit Christian Albrechts Universität, Kiel, Deutschland und der ‚the European Society for Gynaecological Endoscopy' (ESGE). 18.- 22. Feb 2007.**
- Annual International Meeting of the Department of Obstetrics and Gynaecology, Alexandria University. Abteilung der Frauenheilkunde und Geburtshilfe, Alexandria Universität. Mai 2005, Mai 2006, April 2007 und April 2008.

ZERTIFIKATE UND ABSCHLÜSSEN

- **Schwerpunkt ‚Gynäkologische Onkologie'** beantragt an der bayerischen Landesärztekammer, 24.04.2013.
- **Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)** Mitgliedschaft beantragt 23.04.2013.
- **Deutsche Krebs Gesellschaft (DKG)** Mitglied ab 22.04.2013.
- **MIC I Zertifikat. AGE.** 20. März 2013.
- **Arbeitsgemeinschaft Gynäkologische Endoskopie (AGE)** Mitglied ab 09.01.2013.
- **Deutsche Gesellschaft für Klinische Mikrozirkulation und Hämorheologie (DGKMH)** Mitglied ab Januar 2013.
- **Approbation als Arzt** in Deutschland (Bezirksregierung Detmold) ab 02.04.2012.
- **Facharzt für Frauenheilkunde und Geburtshilfe. Ärztekammer Westfalen-Lippe** 19 November 2011.
- **DGGG** Mitglied ab Dez 2011.
- **IGCS** Mitglied ab Juli 2010.
- **DAAD** Stipendiat ab März 2009.
- **Facharzt für Frauenheilkunde und Geburtshilfe, ägyptisches medizinisches Syndikat (ägypitsche Ärztekammer)** ab 4 April 2007
- **Approbation als Arzt, ägyptisches medizinisches Syndikat (ägyptische Ärztekammer)** ab 12 Marz 2003

PUBLIKATIONEN UND PATENTE

- **Soliman AA**, Csorba R, Ullricha A, Tsikouras P, von Tempelhoff G-F. **Antiphopholipid antibodies and functional activated protein C resistance in breast cancer patients during anthracycline based chemotherapy administered through an intravenous port-catheter device.** J Thromb Haemost. Submitted.
- **Soliman AA**, Csorba R, Tsikouras P, Wieg C, Harnack H, von Tempelhoff G-F. **Neonatal blood rheological parameters at delivery in healthy neonates and in those with morbidities.** Clin Hemorheol Microcirc. Epub 26.03.2013.
- **Soliman AA**, Csorba R, Yilmaz A, von Tempelhoff G-F. **Rheologic results and their correlation to hemostatic changes in patients with moderate and severe preeclampsia; an observational cross-sectional study.** Clin Hemorheol Microcirc. Epub 22.10.2012.

- Wojcinski S, **Soliman AA**, Schmidt J, Makowski L, Degenhardt F, Hillemanns P. **Sonographic features of triple-negative and non-triple-negative breast cancer.** J Ultrasound Med. 2012; 10:1531-1541.
- **Soliman AA**, Wojcinski S, Degenhardt F. **The Effect of Accompanying In-Situ Ductal Carcinoma on Accuracy of Measuring Malignant Breast Tumor Size Using B-Mode Ultrasonography and Real Time Sonoelastography**. Int J Breast Cancer. 2012; 2012:376032.
- **Soliman AA**, Degenhardt F, Wojcinski S. **Möglickeiten der Sonographie beim Endometriumkarzinom** gynäkologische praxis. 2012; 36: 67-78.
- **Soliman AA,** Heubner M, Kimmig R, Wimberger P**. Morbidity of inguino-femoral lymphadenectomy in vulval cancer.** ScietificWorldJournal. 2012:341253. Epub 2012 Jan 4.
- Wojcinski S, Cassel M, Farrokh A, **Soliman AA**, Hille U, Schmidt W, Degenhardt F, Hillemanns P. **Variations in the elasticity of breast tissue during the menstrual cycle determined by real-time sonoelastography.** J Ultrasound Med; 2012 Jan;31(1):63-72.
- **Soliman AA**, ElSabaa B, Hassan N, Sallam H and Ezzat T. **Degenerated Huge Retroperitoneal Leiomyoma presenting with sonographic features mimicking a large uterine Leiomyoma in an infertile woman with history of myomectomy: a case report.** J of Med Case Reports. 2011, **5(1)**:578
- Wojcinski S, Farrokh A, Hille U, Wiskirchen J, Gyapong S, **Soliman AA**, Hillemanns P, Degenhardt F. **The Automated Breast Volume Scanner (ABVS): Initial Experiences in Lesion Detection Compared to Conventional Handheld B-Mode Ultrasound (HHUS): A Pilot Study of 50 Cases.** Int J Womens Health. 2011;3:337-46.
- **Soliman AA**, Said T. **Insulin-like Growth Factor Binding Protein-1, is it the real gold standard for detecting PROM?** Down's Screening News. DSNews 2009;15(1): 23.
- Aboul Enien WM, Azzam AZ, Saleh FM, Abo Ollo M, **Soliman AA**. **Evaluation of Insulin-like Growth Factor Binding Protein-1 (IGFBP-1) in cervicovaginal secretions as an indicator of premature rupture of membranes: a comparison with Nitrazine test and Amniotic Fluid Index.** Arab J Lab Med 2006;32,3:385-97.

POSTER UND ORAL VORTRÄGE BEI KONGRESSE

- **Amr Soliman. Stand der endokrinen Therapie beim Mammakarzinom- Neues aus San-Antonio 2012.** Fortbildungsveranstaltung der Frauenklinik, Klinikum Aschaffenburg, 19.12.2012, Großostheim.
- **Soliman AA**, Heubner M, Kimmig R, Wimberger P. **Factors affecting the development of local complications of inguino-femoral lymphadenectomy in vulval cancer.** Oral Presentation. XX FIGO World Congress of Gynecology and Obstetrics, 07.-12.10.2012, Rom, Italien.
- **Soliman AA**, Wojcinski S, Degenhardt F. **Ultrasonographic examination of the endometrium and myometrium using acoustic radiation force impulse (ARFI) imaging technology: Implications of a new method.** Oral Presentation. XX FIGO World Congress of Gynecology and Obstetrics, 07.-12.10.2012, Rom, Italien.
- **Soliman AA**, Heubner M, Kimmig R, Wimberger P. **Morbidity of inguino-femoral lymphadenectomy in vulval cancer.** Poster #324 (late breakers) Proceedings of the 17th International Meeting of the European Society of Gynecological Oncology, Milan, Italy, 11-14 September 2011.

- Tamer H. Said, Mohamed Rocca, Aly Kholif, Ahmed I Ahmed, **Amr Soliman**, Paul C. Magarelli. **Ovarian reserve after surgical treatment of unilateral benign ovarian cyst** fertil steril 2009; 91,3(S1): S20.
- Tamer H. Said, Ahmed I Ahmed, Mohamed Rocca, Aly Kholif, **Amr Soliman**, Paul C. Magarelli. **Effect of body mass index on post cystectomy ovarian reserve markers** fertil steril 2009; 91,3(S1): S21.
- **Soliman AA**, Aboul Enien WM., Azzam AZ, Saleh FM, Abo Ollo M. **Detection of IGFBP-1 in Cervicovaginal Secretions in Cases of Premature Rupture of Membranes; Comparison with Nitrazine Test and Ultrasonic Amniotic Fluid Volume Assessment.** Poster #5. Proceedings of the 7th World Congress of Foetal Medicine. Sorrento, Italy, June 22nd-26th, 2008.
- **Soliman AA**, Aboul Enien WM., Azzam AZ, Saleh FM, Abo Ollo M. **Detection of IGFBP-1 in Cervicovaginal Secretions in Cases of Premature Rupture of Membranes; Comparison with Nitrazine Test and Ultrasonic Amniotic Fluid Volume Assessment.** Poster #5. Proceedings of the 7th World Congress of Foetal Medicine. Sorrento, Italy, June 22nd-26th, 2008.

WISSENSCHAFTLICHES GUTACHTEN

- Reviewer. International Journal of Women's Health. 2012.

REFERENZEN

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