



Thromboelastometry: studying hemostatic profile in small for gestational age neonates—a pilot observational study

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Abstract

Scarce data exists about the hemostatic status of small for gestational age (SGA) neonates. We aimed at evaluating the hemostatic profile of SGA neonates, using thromboelastometry (TEM). This is an observational study performed in a Greek tertiary General Hospital during an 18-month period. Ninety-three neonates were included in the study: 48 appropriate for gestational age weight (AGA) neonates and 45 SGA neonates. Extrinsically activated TEM (ex-TEM) parameters, such as clotting time, clot formation time, amplitude recorded at 5 and 10 min, a angle, maximum clot firmness, lysis index at 60 min, and also platelet count, were used for the evaluation of the hemostatic profile in all neonates. No statistically significant differences were noticed regarding all ex-TEM parameters between AGA and SGA neonates, while no event of hemorrhage or thrombosis was noticed in the study population.

Conclusions: The coagulation system of SGA neonates seems to be fully functional, with no evident tendency toward coagulopathy or thrombosis, when compared with AGA neonates. TEM seems to provide a promising and valid assessment of coagulation and fibrinolysis systems and may be used as a valuable biomarker, in the future. Further studies, with large samples, are necessary to confirm our results.

Rozeta Sokou and Aikaterini Konstantinidi contributed equally to this work.

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What is Known:

- SGA neonates may present coagulation disorders mainly due to hepatic dysfunction, polycythemia, and thrombocytopenia owing to long-term intrauterine hypoxia.
- In the literature, despite the statistically significant differences in laboratory results between SGA and AGA neonates, no clinical manifestations of significantly altered hemostasis were recorded. Data of TEM interpretation of hemostasis in SGA neonates are not available.

What is New:

- TEM seems to interpret coagulation mechanism of preterm and full-term SGA neonates and confirm previous relevant literature findings regarding hemostasis in these neonates.

Keywords Hemostasis · SGA neonates · Thromboelastometry · Coagulation system · Coagulation disorders

Abbreviations

A5, A10	Amplitude recorded at 5 and 10 min
AGA	Appropriate for gestational age
a°	a angle
APCR	Activated protein C resistance
aPTT	Activated partial thromboplastin time
AT-III	Antithrombin III
CFT	Clot formation time
CT	Clotting time
DOL	Day of life
ex-TEM	Extrinsically activated TEM
GA	Gestational age
INR	International normalized ratio
IQR	Interquartile ranges
LI60%	Lysis index at 60 min
MCF	Maximum clot firmness
nCPAP	Nasal continuous positive airway pressure
NICU	Neonatal Intensive Care Unit
PAI-1	Plasminogen activator inhibitor-1
PEEP	Pressure positive end-expiratory pressure
POC	Point-of-care
PT	Prothrombin time
SGA	Small for gestational age
TEG	Thromboelastography
TEM	Thromboelastometry
tPA	Tissue plasminogen activator

Introduction

Coagulation system gradually matures throughout infancy until adulthood. Healthy neonates are born with an intrinsic hemostatic deficit directly dependent on gestational age, birth weight, and maturation of hepatic function. All factors of the coagulation–fibrinolysis system are immature in neonates when compared with infants, children, or adults. However, studies have shown that this immaturity is functionally counterbalanced and therefore the risk for hemorrhage or thrombosis is not increased in healthy full-term or preterm newborns [18]. This delicate hemostatic balance is deranged in sick neonates, predisposing to hemorrhage and/or thrombosis.

Small for gestational age (SGA) neonates may present coagulation disorders mainly due to hepatic dysfunction, polycythemia, and thrombocytopenia owing to long-term intrauterine hypoxia [9]. Available data in the literature are heterogeneous and rather vague regarding this certain population. Most studies revealed prolongation of prothrombin time (PT), elevated levels of international normalized ratio (INR), tissue plasminogen activator (tPA), decreased values of factor XII, and free protein S in SGA neonates, without associated clinical manifestations due to altered hemostasis [5].

The evaluation of hemostatic parameters in SGA neonates will facilitate diagnosis of coagulation disorders in these newborns. However, laboratory diagnosis in neonates may be difficult to establish because of the need to adapt laboratory tests to the smaller sample volumes obtained. Age-related changes in hemostatic profile complicate furthermore the interpretation of common laboratory tests such as PT, activated partial thromboplastin time (aPTT), platelet count, and bleeding time. Because of these limitations, point-of-care (POC) sample collections are optimal, but scarce [2].

Thromboelastography (TEG) and thromboelastometry (TEM) represent the currently available methods for assessing clot formation by using whole blood and limited sample volumes. They monitor viscoelastic changes during coagulation in whole blood and provide values for the entire hemostatic process, allowing for assessment of all aspects of the hemostatic system [7, 10, 17]. There are limited data on normative ranges for TEM parameters in newborns, and most of them refer to cord blood samples. A recent study established local reference ranges for the standard extrinsically activated TEM (ex-TEM) assay in peripheral whole blood samples of normal full-term and preterm neonates, without statistically significant differences between them, except for the lysis index [15]. To the best of our knowledge, there are no reports of coagulation studies using viscoelastic methods to evaluate hemostatic parameters in SGA neonates.

The present study aimed to evaluate the hemostatic status of SGA neonates using TEM.

Methods

Study design—setting

This observational study was conducted from July 2014 up to February 2016 at the Neonatal Intensive Care Unit (NICU) of the Nikaia-Piraeus General Hospital “Aghios Panteleimon.”

Participants

The study included a convenient sample of term and preterm neonates born at the obstetric unit of the above mentioned hospital or hospitalized in the NICU of the same hospital. Preterm neonates with respiratory distress syndrome (RDS) were included in our study after weaning from mechanical ventilation and stabilization (room air for preterms of 32–36 gestational weeks; nasal continuous positive airway pressure (nCPAP) with FiO_2 0.21 and pressure positive end-expiratory pressure (PEEP) 5 cm H_2O for the preterms < 32 gestational weeks).

Exclusion criteria included the following. (1) Newborns (terms and preterms) with a personal or family history of bleeding disorders, known or suspected major chromosomal anomaly, suspected or confirmed sepsis, perinatal blood loss, and birth asphyxia. (2) Neonates with a documented significant bleeding event or with a history of blood, platelets, fresh frozen plasma, or cryoprecipitate transfusion. Significant bleeding was defined as any clinically overt bleeding of mucosal membranes, respiratory, gastrointestinal, or urinary tract, which (i) was associated with a drop in hemoglobin level of ≥ 2 g/dl in a 24-h period and/or (ii) required surgery or blood, platelets, fresh frozen plasma, or cryoprecipitate transfusion. (3) Moderate or severe acidemia.

All neonates received 1 mg of vitamin K intramuscularly immediately after delivery and were followed up until hospital discharge and up to 18 months of age. We performed brain and abdomen ultrasound in all neonates according to our NICU protocol weekly and whenever a bleeding or thrombotic event was suspected.

The neonates were categorized in two groups: neonates with appropriate for gestational age weight (AGA) (group A) and neonates with small for gestational age weight (group B). SGA newborns are defined as having a birth weight below the 10th percentile for gestational age (GA), while AGA newborns have birth weight ranging between the 10th and 90th percentiles, according to the birth weight for GA curve determined by Fenton et al. [3].

Variables—measurements

Clinical data regarding gestational age, gender, delivery mode, pregnancy type (single, twin), maternal medical history, and

complications during hospitalization, either in the obstetrics unit or in the NICU, were recorded.

Blood samples were collected from preterm neonates hospitalized in our NICU on the 2nd to 7th day of life (DOL). In respect to term neonates, the blood sample was collected on the 2nd to 3rd DOL and each blood collection was performed due to other medical reasons (i.e., hyperbilirubinemia, testing for ABO incompatibility or testing of neonates born to mothers without prenatal care). The collection of the samples and the performance of the ex-TEM test were carried out by two experts operators in performing TEM (RS, AK).

Arterial blood was drawn via peripheral artery by using a 23G-0.6 mm needle, collected into citrated tube (0.109 mol/l trisodium citrate) by a vacutainer system and stored at room temperature until testing. The citrated arterial blood (300 μl) was incubated for 2–5 min at 37 °C and was tested by the ROTEM analyzer (Tem Innovations GmbH, Munich, Germany) in < 30 min following blood collection. The ex-TEM tests were performed in single determination using the respective automated pipette programs according to the instructions of the manufacturer. Clot formation was induced by activation of the extrinsic coagulation pathway using 20 μl of 0.2 M calcium chloride solution (star-TEM reagent) and 20 μl of extrinsic activator (ex-TEM reagent). After the reagents were adequately mixed, 300 μl of citrated whole blood was added to the cup and the assay was running for at least 60 min after the completion of clot lysis at 30 min. As part of the routine process, blood specimens were carefully checked for fibrin clots and other contaminating materials. In such a case, the specimen was discarded.

The following ex-TEM variables were measured: clotting time (CT, seconds), the time from the beginning of measurement until the formation of a clot 2 mm in amplitude; clot formation time (CFT, seconds), the time from CT (amplitude of 2 mm) until a clot firmness of 20 mm was achieved; amplitude was recorded at 5 and 10 min (A5, A10, mm); a angle (α°), the angle between the central line (x-axis) and the tangent of the TEM tracing at the amplitude point of 2 mm, describing the kinetics of clot formation; maximum clot firmness (MCF, mm), the final strength of the clot; and lysis index at 60 min (LI60, %), the percentage of remaining clot stability in relation to the MCF following the 60-min observation period after CT which indicates the speed of fibrinolysis.

Bias

We compared all the above mentioned measurements between AGA and SGA neonates. This study is cross-sectional in nature. Consequently, effort was made to avoid selection bias, by including a sample of healthy neonates of the obstetrics unit, thus attaining a representative sample, and excluding participants with clinical entities, considered as confounding factors. Information bias was ruled out by using standardized and

validated methods for reporting the results (STROBE statement for case–control studies [19] and the broader EQUATOR guidelines [14]).

Statistical analysis

Descriptive statistics are presented as medians and interquartile ranges (IQR) or percentages when appropriate. Because most of the variables were non-normally distributed, nonparametric tests (the Pearson's chi-squared test, the Fisher's exact test, and the two-sample Wilcoxon rank-sum (Mann–Whitney test)) were used for the statistical evaluations. Correlations were evaluated by the Spearman rank correlation coefficient and the respective *p* value. For hypothesis testing, a probability level of <0.05 was considered to be statistically significant. All statistical tests were two-sided. The R software, version 3.5.1 was used for all statistical analyses.

Results

Over an 18-month period, 110 neonates were evaluated. Eventually, study population consisted of 48 AGA and 45 SGA neonates since 17 neonates (10 AGA neonates (6 of them were preterm) and 7 SGA neonates (4 preterm infants)) were excluded due to improper blood sampling. Thus, the SGA group included 23 term (mean GA 38.17 ± 1.19 weeks), and 22 preterm neonates (mean GA 34.14 ± 1.91 weeks), while the AGA group included 23 term (mean GA 38.13 ± 1.06 weeks) and 25 preterm neonates (mean GA 34.44 ± 1.78 weeks). All recruited neonates were stable and clinically healthy at the time of the sampling. There was no incidence of infection or sepsis, disseminated intravascular coagulopathy, necrotizing enterocolitis, congenital malformation, perinatal hypoxic stress, and acute renal malformation in the study

population. Moreover, no bleeding or thrombosis event was recorded in all neonates with regard to clinical, laboratory, and radiological follow-up. Demographic data and clinical characteristics are summarized for both groups in Table 1. Although infants born SGA are at higher risk for renal insufficiency, manifested by serum creatinine elevation during the first week of life, no statistical difference was noticed regarding this biochemical parameter between SGA and AGA neonates. Basic blood test parameters are presented in Table 2. Platelet count was found to be significantly lower in SGA neonates. No significant statistical differences were noticed with regard to CT, CFT, A5, A10, α angle, MCF, and LI60 between AGA and SGA neonates (Table 3). Stratified analysis showed that there were no differences in any of ex-TEM parameters when the population was stratified by delivery time; thus, prematurity is not a confounding factor (Table 4). Moreover, there was no statistically significant difference in ex-TEM parameters between SGA preterm and term neonates (Table 5). Finally, no significant correlations were found between any of basic blood parameters, including hematocrit, with any of the ex-TEM parameters.

Discussion

To the best of our knowledge, this study was the first to report on the evaluation of the hemostatic profile of SGA neonates using TEM. No significant statistical differences were found between SGA and AGA neonates in all measured TEM parameters, while at the same time, no major or minor hemorrhagic or thrombotic event was noticed in the study population until hospital discharge and up to 18 months of age.

Hemostasis balances pro- and anticoagulant forces in order to protect against uncontrolled bleeding, after vascular injury, while simultaneously prevents excessive clotting. The

Table 1 General characteristics of AGA (group A) and SGA (group B) neonates

		Total sample	AGA (<i>n</i> = 48)	SGA (<i>n</i> = 45)	<i>p</i> value
Gestational age	Pre-terms	47 (50.5%)	25 (52.1%)	22 (48.9%)	<i>p</i> = 0.75
	Full terms	46 (49.5%)	23 (47.9%)	23 (51.1%)	
Gender (females)		47 (50.5%)	29 (60.4%)	18 (40.0%)	<i>p</i> = 0.049
Birth weight (grams)		2430 (2100–2745)	2700 (2415–3100)	2120 (1800–2390)	<i>p</i> < 0.001
Delivery mode	Natural	33 (35.5%)	21 (43.8%)	12 (26.6%)	<i>p</i> = 0.085
	Cesarean section	60 (64.5%)	27 (56.3%)	33 (73.3%)	
Pregnancy type	Single	80 (86.0%)	42 (87.5%)	38 (84.4%)	<i>p</i> = 0.67
	Twin	13 (14.0%)	6 (12.5%)	7 (15.6%)	
IUGR		39 (41.9%)	–	39 (86.7%)	NA
IVH		–	–	–	NA

Data are presented as percentages or medians and interquartile ranges in parentheses when appropriate. Nonparametric tests (the chi-squared test, Fisher's exact test and the two-sample Mann–Whitney test) were used for the statistical evaluations

AGA appropriate for gestational age, SGA small for gestational age, IVH intraventricular hemorrhage, IUGR intrauterine growth restriction, NA not applicable

Table 2 Comparison of blood test parameters between AGA and SGA groups

Variable	Total sample	AGA <i>n</i> = 48	SGA <i>n</i> = 45	<i>p</i> value
Days of blood sampling	3 (2–4.5)	3 (2–4)	3 (2–5)	<i>p</i> = 0.32
WBC count	10,370 (8690–12,430)	10,500 (8730–15,420)	10,220 (8660–11,582)	<i>p</i> = 0.43
PLTs count	203,000 (156000–274,000)	246,000 (203000–307,500)	169,000 (137000–237,000)	<i>p</i> < 0.001
CRP (mg/l)	1 (0.5–1.6)	1.15 (0.6–1.9)	0.7 (0.5–1.5)	<i>p</i> = 0.17
AST (mg/dl)	38 (30.2–52.5)	38 (31.5–59)	40.5 (29.7–50.2)	<i>p</i> = 0.84
ALT (mg/dl)	12 (9–15)	12 (10.5–15.5)	11 (7.8–15)	<i>p</i> = 0.24
Total bilirubin (mg/dl)	5.9 (3.9–8.3)	6.3 (4.4–11.7)	5.5 (3.8–7.6)	<i>p</i> = 0.11
Direct bilirubin (mg/dl)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.3 (0.2–0.3)	<i>p</i> = 0.52
BUN (mg/dl)	21 (10–35)	22 (12–36.5)	19.5 (10–34.2)	<i>p</i> = 0.51
Creatinine (mg/dl)	0.6 (0.4–1)	0.6 (0.4–0.8)	0.7 (0.4–1)	<i>p</i> = 0.25

Data are presented as medians and interquartile ranges in parentheses. The nonparametric two-sample Mann–Whitney test was used for the statistical evaluations

AGA appropriate for gestational age, SGA small for gestational age, WBC white blood cells, PLTs platelets, CRP C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, BUN blood urea nitrogen

physiologic system of hemostasis seems to be functionally immature at birth. It is progressively developed throughout infancy, and childhood until adulthood. While the key factors of this physiologic system are present at birth, they exhibit quantitative and qualitative differences, observed in numerous studies in populations of various age ranges. These age-related changes are not considered as coagulation disorders, but they are elements of normal physiological development [11]. Although reference ranges exist for procoagulant and anticoagulant factor plasma levels and standard coagulation tests (PT, PTT, INR, platelet counts, and fibrinogen) in newborns, there are still no reliable tests to assess the entire hemostatic status surrounding bleeding and thrombosis in patients with coagulation disorders, possibly because these tests fail to

encompass the important cellular interactions that take place during hemostasis [13].

On the contrary, TEG/TEM do reflect, in a single functional test, the complex interactions between coagulation factors, cellular components, and enzymes that maintain equilibrium between clot formation and lysis [15]. These characteristics make this method particularly attractive to evaluate coagulopathy in the critically ill newborns, including asphyxiated or septic [16].

Regarding term SGA newborns, Perlman and Dvilansky were first to report prolonged PT, aPTT, and thrombin time, low platelet count, and increased ratio fibrin/fibrinogen degradation products [8]. Peters et al. observed decreased levels of antithrombin III (AT-III) and a2-antiplasmin in term SGA newborns in relation to AGA infants [9]. Mitsiakos and colleagues found significant prolongation in PT and INR, elevated levels of tPA, decreased values of FXII, and free protein S in SGA in comparison to AGA full term neonates [5], while significantly lower levels of fibrinogen and higher levels of VIII coagulant activity (VIIIc) factor, activated protein C resistance (APCR), tPA, and plasminogen activator inhibitor-1 (PAI-1) were observed in premature SGA compared to AGA premature neonates [6]. In all these studies, despite the statistically significant differences in laboratory results between SGA and AGA neonates, no clinical symptoms or signs of significantly altered hemostasis were recorded in subject populations.

In our study, there were no significant statistical differences in all ex-TEM parameters between SGA and AGA neonates in both term and preterm groups. A trend to prolonged CFT was noticed in term and preterm SGA neonates, possibly due to their lower plasma factor levels [4] in accordance with prolonged PT and aPTT reported in previous studies [5, 8]. It is also noteworthy that despite significantly higher platelet counts observed in AGA compared with SGA neonates, no

Table 3 Comparison of ex-TEM parameters between AGA and SGA groups

Ex-TEM parameters	AGA <i>n</i> = 48	SGA <i>n</i> = 45	<i>p</i> value
CT (s)	43 (37.5–48.0)	44 (38.0–51.0)	<i>p</i> = 0.36
CFT (s)	65 (50.0–87.0)	68 (55.0–100.5)	<i>p</i> = 0.29
A5 (mm)	50 (44.0–55.0)	49 (38.5–54.5)	<i>p</i> = 0.45
A10 (mm)	59.5 (53.5–63.5)	59 (49.5–64.0)	<i>p</i> = 0.43
MCF (mm)	66 (61.5–71.0)	65 (59.5–70.0)	<i>p</i> = 0.54
A angle (°)	79 (74.5–81.5)	78 (71.0–80.0)	<i>p</i> = 0.18
LI60 (%)	97 (93.0–99.0)	97 (94.0–100.0)	<i>p</i> = 0.21

Data are presented as medians and interquartile ranges in parentheses. The nonparametric two-sample Mann–Whitney test was used for the statistical evaluations

SGA small for gestational age, CT clotting time, A5 clot amplitude at 5 min, A10 clot amplitude at 10 min, CFT clot formation time, MCF maximum clot firmness, Alpha a angle, LI60 lysis index at 60 min

Table 4 Stratification by delivery time and comparison of ex-TEM parameters between AGA and SGA neonates

Ex-TEM parameters	Term neonates			Preterm neonates		
	AGA	SGA	<i>p</i> value	AGA	SGA	<i>p</i> value
CT (s)	44 (39–54)	41 (39–46)	<i>p</i> = 0.81	43 (35.5–47)	45 (37–51)	<i>p</i> = 0.11
CFT (s)	66 (55–102)	73 (62–98)	<i>p</i> = 0.52	59 (46.5–80)	64 (49–103)	<i>p</i> = 0.51
A5 (mm)	48 (39–52)	45 (39–53)	<i>p</i> = 0.84	52 (46–58)	50.5 (38–58)	<i>p</i> = 0.61
A10 (mm)	59 (49–61)	55 (49–61)	<i>p</i> = 0.70	61 (56–66.5)	60.5 (52–67)	<i>p</i> = 0.66
MCF (mm)	65 (60–69)	65 (60–69)	<i>p</i> = 0.82	68 (62–73)	66.5 (57–71)	<i>p</i> = 0.38
Alpha (°)	77 (73–81)	77 (70–80)	<i>p</i> = 0.35	80 (75.5–82)	78 (74–82)	<i>p</i> = 0.38
LI60 (%)	97 (94–99)	97.5 (94–100)	<i>p</i> = 0.27	95 (92–98)	96 (93–100)	<i>p</i> = 0.46

Data are presented as medians and interquartile ranges in parentheses. The nonparametric two-sample Mann–Whitney test was used for the statistical evaluations

SGA small for gestational age, CT clotting time, A5 clot amplitude at 5 min, A10 clot amplitude at 10 min, CFT clot formation time, MCF maximum clot firmness, Alpha a angle, LI60 lysis index at 60 min

significant difference was found between A5, A10, and MCF in the two groups. Thus, thrombocytopenia, which is very common among SGA neonates [1], does not seem to affect clot firmness. The prevalence of IUGR within the SGA infants is high in the present study. Coagulation abnormalities in the IUGR are mainly characterized by the shift of the hemostasis balance toward thrombosis, and although the underlying mechanism is not clear, polycythemia/hyperviscosity and alterations in vascular structure and function may be significant triggering factors. TEG measurements performed in adult patients with polycythemia/hyperviscosity show hypercoagulable state due to thrombocytosis rather than the plasma factors [12]. On the contrary, in our study, TEM measurements did not demonstrate hypercoagulability in SGA neonates probably due to the thrombocytopenia detected in them.

Ex-TEM results also corresponded with clinical, laboratory or radiological findings, as we did not observe any signs of hemorrhage or thrombosis in any of the neonates included in the study. Moreover, ex-TEM parameters did not differ to a

significant level between term and preterm SGA infants. This finding is in keeping with the results of another study by our research group, demonstrating similar values for all ex-TEM parameters (except LI60) between term and preterm AGA neonates [15].

Certain limitations need to be acknowledged. As this is a pilot study with no preexisting ex-TEM data from SGA neonates available, a sample size calculation is missing. TEM was the single assay performed in the blood samples, and there was no correlation to other standard coagulation tests, due to the practice of minimal handling of the neonates and the limited volume of residual blood. The high incidence of IUGR within the SGA infants may also represent a bias and, finally, caution needed for extracting conclusion when comparing preterm and term SGA neonates due to the small number of cases.

In conclusion, TEM, providing a global functional assessment of hemostatic mechanism, seems to interpret and confirm previous relevant literature findings regarding hemostasis in SGA neonates. Their coagulation system is functionally effective, with no tendency toward coagulopathy or thrombosis, compared to AGA neonates. Although further large-scale comparative studies are necessary to verify these findings, this study may be useful in understanding coagulation mechanism of preterm and full-term SGA neonates.

Authors' contributions RS, AK, and AT contributed to the conception and design of the study. RS, AK, SP, KL, GK, EK, and ET conducted the work and collected the data. A.G.T, AK, CS, RS, and SB carried out the statistical analysis. All authors contributed to the interpretation of data for the work. RS, AK, AT, SP, NI, AG, and SB drafted the manuscript. All authors critically revised the paper for important intellectual content and approved the final version to be published.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Table 5 Comparison of ex-TEM parameters between term SGA and preterm SGA neonates

Ex-TEM parameters	Term SGA <i>n</i> = 23	Preterm SGA <i>n</i> = 22	<i>p</i> value
CT (s)	41 (39–46)	45 (37–51)	<i>p</i> = 0.65
CFT (s)	73 (62–98)	64 (49–103)	<i>p</i> = 0.28
A5 (mm)	45 (39–53)	50.5 (38–58)	<i>p</i> = 0.17
A10 (mm)	55 (49–61)	60.5 (52–67)	<i>p</i> = 0.11
MCF (mm)	65 (60–69)	66.5 (57–71)	<i>p</i> = 0.92
A angle (°)	77 (70–80)	78 (74–82)	<i>p</i> = 0.25
LI60 (%)	97.5 (94–100)	96 (93–100)	<i>p</i> = 0.40

Data are presented as medians and interquartile ranges in parentheses. The nonparametric two-sample Mann–Whitney test was used for the statistical evaluations

SGA small for gestational age, CT clotting time, A5 clot amplitude at 5 min, A10 clot amplitude at 10 min, CFT clot formation time, MCF maximum clot firmness, Alpha a angle, LI60 lysis index at 60 min

Informed consent For this type of study, formal consent is not required.

Ethical approval The study was conducted in agreement with the Helsinki Declaration. Ethical approval was obtained from the Research Ethics Committee of the General Hospital of Nikaia-Piraeus “Aghios Panteleimon” (15.07.2014, 32/3).

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