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# Analyzing The Role of Rotational Thromboelastometry (ROTEM) in Postpartum Hemorrhage Management, Accounting the Importance of Time and Target

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**ABSTRACT**

Postpartum hemorrhage (PPH) is the most significant cause of mothers' postpartum mortality. Its causes are generally explained as a mnemonic of 4Ts, which include: Tone, Tissue, Trauma, Thrombin. It is of extreme importance to perform timely interventions of both surgical and medical treatments to control PPH, also precise and rapid monitoring of maternal coagulopathies plays a critical role in the treatment process. ROTEM usage as an accurate and rapid tool for coagulation assessment on the maternal bedside is progressing worldwide. This study reviews the most up-to-date papers in this field and has summarized the role of rotational thromboelastometry (ROTEM) to treat PPH effectively and with the least adverse outcomes. At first, we explain the causes of PPH, physiological changes in the coagulation system at term pregnancy (including a significant increase in blood fibrinogen levels) and then we explain the application of ROTEM and its output data on medical practice. We also discuss normal values of ROTEM parameters in term pregnancy and compare the normal parameter ranges with the normal non-pregnant population. Ultimately, the way of approaching the ROTEM output parameters, particularly the FIBTEM A5, has been mentioned as a rapid diagnostic output of ROTEM in most PPH-related coagulopathies. Moreover, we demonstrate the costs and benefits of treatment with fibrinogen concentrate and blood products based on the ROTEM output results. It appears that ROTEM has shown a promising view in the field of obstetrics and gynecology surgeries (especially in the management of PPH) and contrives early therapeutic interventions in parallel with reducing the administration of blood products and their adverse outcomes (TACO, TRALI, …) in mothers, therefore maternal mortality and morbidity due to PPH can be reduced more than before by ROTEM-guidance becoming widespread.

**Keywords:** Fibrinogen, FIBTEM, Postpartum Hemorrhage, ROTEM



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# بررسی کاربرد ترومبوالاستومتری در بهبود سرعت و دقت مدیریت خونریزی پس از زایمان

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## چکیده

خونریزی‌های پس از زایمان مهم‌ترین علت مرگ و میر پس از زایمان در اغلب کشورها محسوب می‌شود و علل اصلی زمینه ساز آن به اختصار شامل چهار مورد است: تون رحم، بقایای بافتی، تروما و آسیبهای زایمانی، اختلالات انعقادی. لذا ارزیابی دقیق و بموقع از وضعیت انعقادی مادر و انجام درمانهای طبی و جراحی زودهنگام نقش مهمی در کنترل خونریزیهای پس از زایمان ایفا میکند. روش آزمایشگاهی روتم که قابلیت انجام سریع بر بالین مادر را دارد، میتواند اطلاعات ارزشمندی درمورد وضعیت انعقادی مادر و نحوه موثر و کم عارضه مدیریت خونریزی پس از زایمان به پزشک ارایه کند و کاربرد آن در زمینه های مختلف کنترل خونریزی در حال گسترش است. در این مقاله مروری چکیده ای از دستاوردهای مطالعات اخیر در این زمینه با نگرش کاربردی گردآوری شده است. ابتدا توضیح اجمالی درمورد تغییرات فیزیولوژیک سیستم انعقادی در حاملگی بیان شده و سپس به معرفی روتم و پارامترهای خروجی آن پرداخته شده و با این مقدمه در مورد کاربرد بالینی این پارامترها در مدیریت خونریزی پس از زایمان و چگونگی اجتناب از عوارض ناخواسته ناشی از تزریق فراورده های خونی و پیشنهادهایی کاربردی در مورد چگونگی تجویز کنسانتره فیبرینوژن در بالین مطرح شده است.

کلید واژه‌ها: فیبرینوژن، خونریزی پس از زایمان، ترومبوالاستومتری چرخشی.

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## Introduction:[1]

Postpartum hemorrhage (PPH) definition has been accepted by most physicians as the hemorrhage volume of more than 500 ml in vaginal delivery and more than 1000 ml in cesarean section. Primary PPH is defined as maternal hemorrhage in the first 24 hours after delivery, which is the most significant cause of maternal mortality [1,2]. In these cases, surgical and medical treatments should be considered based on the maternal condition (such as repeatedly uterotonic administration, removal of retained placental remnants, and repairing the hemorrhagic trauma to the childbirth canal). On the other hand, it is significantly important to evaluate maternal coagulopathies and make timely, effective, and with the least complication possible treatment interventions.

The causes of PPH are also classified as 4T mnemonics, including Tone, Tissue, Trauma, Thrombin. Among these causes, uterine atony with 80% prevalence is the most prevalent cause of PPH, which its treatment is based on uterotonic administration. The concentration of most coagulation factors, including fibrinogen, is increased physiologically during pregnancy, which, despite the increased risk of thromboembolism in pregnancy, conduces almost all mothers to physiologically compensate the regular delivery bleeding without the need for any specific treatment. Paying attention to potential maternal coagulopathies is a lost key in the approach to postpartum hemorrhage [3].

Fibrinogen consumption plays a major role in peripartum hemorrhage, and blood fibrinogen levels less than 200 mg/dl at the time of hemorrhage are directly related to hemorrhage severity [4]. While blood fibrinogen levels higher than 400 mg/dl suggest that progression to severe PPH is improbable [5,6]. Therefore, recent studies have recommended that the blood fibrinogen level should be maintained at least 200 mg/dl, and its decline should be prevented [7,8].

Studies have indicated that the quality and speed of clot formation is recognizable in rotational thromboelastometry (ROTEM) parameters even before creating the clinical manifestations of hemorrhagic and dilutional coagulopathies following severe hemorrhage and resuscitation with large volumes of crystalloids in these patients. Hence, makes it possible to preemptively assess the patients' coagulation status and to manage the PPH pertinently with the least complications, and prevent the PPH deterioration to DIC. This study aims to review the most recent studies in this field and summarize the applied methods through the approach of utilizing ROTEM in PPH crisis management.

## Research methodology

In this study, we have tried to evaluate the ROTEM's benefits in mothers' bedside and managing the challenges of delivery by reviewing the related studies which have been published from 2010 to 2021 in well-known medical databases on this era and analyze their results practically.

## Some of ROTEM output parameters at a glance:

ROTEM/TEG involves a set of viscoelastic and elastogram techniques that test the coagulation process of whole blood from various dimensions and can be performed very quickly on the mothers' bedside in addition to demonstrate both quantitative and qualitative images of underlying coagulopathies. Mixing the patient's blood with specific reagents (to evaluate the respective coagulation pathway) is the basis of ROTEM function. ROTEM output parameters are as follows:

EXTEM: Activates the external coagulation pathway by adding the tissue factor to the blood sample.
INTEM: Activates the internal coagulation pathway by adding "ellagic acid" to the blood sample: Activates fibrin-based coagulation process by adding "cytochalasin D" and platelet inhibitor agent to the blood sample. Outputs of each modality are reported as CT & CFT in seconds, α angle which shows the clot formation velocity, values of A5 & A10 & A20, and MCF in millimeters.

EXTEM A10 is a function of the performance of the two coagulative variables fibrinogen and platelet, while FIBTEM A10 solely evaluates fibrinogen function by removing the effect of platelets (a platelet inhibitor is added as a reagent). CT (clotting time) is the time needed for the needle inside the sample cup (which oscillates with a range of 2 mm) to sense and

[1] **Abbreviations:**
PPH: Postpartum Hemorrhage
ROTEM: Rotational Thromboelastometry
CT: Clotting Time
CFT: Clot Formation Time
MCF: Maximum Clot Firmness
MCE: Maximum Clot Elasticity
A10: Clot amplitude at 10 minutes at the end of CT
FC: Fibrinogen Concentrate
FFP: Fresh Frozen Plasma
TACO: Transfusion Acquired Circulatory Overload
TRIM: Transfusion Related Immunomodulation
TRALI: Transfusion Related Acute Lung Injury
TXA: Tranexamic Acid
IUFD: Intra Uterine Fetal Death
PCC: Prothrombin Complex Concentrate





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report clot formation, and this time is normally reported by a range of 43-82 seconds. The α angle can be measured 30-40 seconds after CT completion. It is determined in less than two minutes and is proportional to the clot formation speed. This angle is normally reported for EXTEM, and its normal range is α EXTEM=65°-80°. α FIBTEM>50° is inferred normal and equivalent to A10 FIBTEM above 10 mm. Other parameters, including A10, A20, MCF are reported a few minutes later. Although MCF needs more than 30 minutes to be reported (equivalent to A30-50).

**Some of ROTEM output parameters at a glance:**

In the study done by Toffaletti et al. [9] A10 FIBTEM less than 10 mm has been considered as fibrinogen deficiency and A10 FIBTEM = 10-12 mm interprets as fibrinogen adequacy. αFIBTEM <50° interprets as consistent with A10 FIBTEM <10mm as well. Another point is that FIBTEM MCF & A10 are both comprehensive parameters so that in addition to showing a sufficient level of plasma fibrinogen, these tests report the elasticity of fibrin-based clot, the quality, and quantity of fibrinogen, and other coagulation factors (such as factor XIII), therefore they provide a comprehensive and realistic assessment of coagulation status [10,11,12].

Low FIBTEM A10 (0-3 mm) is considered to have a strong relationship with critically low fibrinogen levels (<100 mg/dl), which indicates a high possibility of the need for massive transfusion in these patients [13,14]. In a study conducted by Collins et al., fibrinogen and FIBTM have been introduced as predictors of severe PPH [15]. Injection of fibrinogen concentrate in situations of FIBTEM A5<12 mm, which correlates with plasma fibrinogen level <200 mg/dl, has been proven efficient in studies that have been conducted to determine the optimal FC injection threshold for therapeutic interventions in PPH [16,17]. Also, the ineffectiveness of FC injection in cases with FIBTEM A5 higher than 15 mm has been confirmed [18].

A group of PPH cases was treated under the direction of ROTEM, and the results were compared with conventional treatment method based on the shock pack algorithms, in a study conducted by McNamara et al. on 32647 deliveries at Liverpool Women's Hospital in the United Kingdom during 4 years [19]. Cases with an estimated hemorrhage of more than 1500 cc or cases with ongoing blood loss accompanied by clinical signs of shock were included in the study. Also, the method of the ROTEM algorithm was planned in such a way that the cases providing A5 FIBTEM=7-12 mm with hemorrhage and all cases with A5 FIBTEM<7 mm have been treated with FC and all of them have been compared with the shock pack method results which are in a case of receiving 4 units of FFP, 4 units of PRBC and one platelet dose. Data have been then compared between the two groups of mothers (variables include: number of injected blood products, the total volume of hemorrhage, the occurrence of TACO, ICU admission, hysterectomy, and death).

Comparing these two groups showed a significant difference in the number of units of injected blood products (*P<0.0001*) and TACO complication due to injection of blood products (*P= 0.002*). FFP was not prescribed at all in the group treated with ROTEM guidance, and there were seen no side effects as well. Furthermore, the need for ICU admission was decreased from 7.7% in the shock pack group to 1.9% in the ROTEM-guided group. The number of hysterectomies was decreased in the ROTEM-guided group (7.9% vs. 13.5%). In mothers with placental abruption, the severity of coagulopathy and fibrinogen depletion magnitude had been much higher than the other causes of PPH. ROTEM has revealed that not all cases of PPH are coagulopathic, and the necessity for treatment with blood products cannot be determined wholly by evaluating the patient's blood loss volume and clinical symptoms because, on the one hand, it does not seem to improve outcomes but will lead to over-treatment and increased rate of complications. On the other hand, these cases can be recognized earlier by ROTEM guidance and can be treated by Individualized treatment of coagulopathy case by case in mothers that coagulopathy is developing but has not yet been clinically revealed. In this study, most of the mothers received a dose of 3 gr of FC and, in some cases, received doses of 6 gr and higher. High doses of 18 gr of FC were administered to mothers with the underlying cause of placental abruption co-occurred by intrauterine fetal death as the PPH etiology. In some cases of placental abruption, extremely low levels of A5 FIBTEM and noticeable prolongation of CT EXTEM over 100 seconds have been reported, despite less apparent hemorrhage in comparison with other PPH etiologies. It is concluded that placental abruption, especially alongside IUFD, provides the most severe cases of coagulopathy among the different PPH etiologies. It has been recommended to keep plasma Fibrinogen levels>200 mg/dl or it is equivalent in the ROTEM in this study, i.e. A5 FIBTEM>12 mm. It is interesting to note that, only 23% of all cases that were included in the study had A5FIB less than 12 mm, and only 54% of these cases required receiving FC due to the continuation of hemorrhage. Other patients' hemorrhage was ceased by eliminating the cause of hemorrhage utilizing surgical homeostasis or receiving uterotonic medications repeatedly. It should



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be stated that the normal level of plasma fibrinogen in term pregnancy is about 400-600 mg/dl (more than double of general population plasma fibrinogen level), and FFP has a fibrinogen concentration equal to 200 mg/dl. Studies have revealed that fibrinogen levels higher than 200 mg/dl are preserved in most mothers with severe PPH, and FFP injection not only does not provide an advantage but can paradoxically reduce maternal fibrinogen levels and intensify coagulopathy and add to the probability of side effects like TACO and ICU admission because fibrinogen in this product is more diluted than maternal plasma itself [20,21].

Only if low levels of A5 FIBTEM are simultaneous with CT EXTEM prolongation, it can be interpreted as insufficiency of other coagulation factors (in addition to fibrinogen insufficiency), and suggest that FFP administration is beneficial for the mother [22]. In this four-year study, only cases with CT EXTEM>100 seconds have been mothers with IUFD-associated placental abruption who had very low A5 FIBTEM at the same time (less than 7 mm) and have received multiple doses of FC (total dose of 18 gr). It is appreciated that PPH had the lowest hemorrhage volume on average with a placental abruption of 2400 ml blood loss, and the placenta accreta with 3500 ml had the greatest hemorrhage volume in terms of the total amount of blood loss based on underlying PPH etiology. To explain this phenomenon one rationalization is that severe coagulopathy is created by occurring placental shearing in the abruption causing the thromboplastin release, which will consume fibrinogen and other coagulation factors and will create a very severe coagulopathy with the clinical manifestation of DIC and therefore, it can be said that the extent of coagulopathy is not necessarily a function of the blood loss volume in PPH, and it is appreciated to certainly notice the underlying cause of PPH as a valuable prognostic measure [23,24]. Studies indicate that level of maternal plasma fibrinogen is above 450 mg/dl on average in most cases of early PPH, and consequently, their plasma fibrinogen levels remain above 200 mg/dl most often (so the volume of bleeding cannot correctly estimate the need to start treatment with FC) and the demand for constant monitoring with ROTEM is felt in terms of rapid monitoring and timely and effective therapeutic interventions [25,26]. A study was conducted on 179 mothers with severe PPH in 2012 [27]. Data were analyzed by determining the area under the curve of maternal plasma fibrinogen and comparing it with the FIBTEM MCF ROTEM output to achieve the proper FC injection threshold number. In mothers, fibrinogen levels were reported to be between 400-600 mg/dl, while fibrinogen is normally in the range of 200-300 mg/dl in non-pregnant populations. This study has reported the FIBTEM MCF ≤18 mm as a suitable threshold with a high positive predictive value. It should be remarked that sufficient time to provide FIB MCF results is estimated to be about 20 minutes, while the blood fibrinogen level measurement needs about 60 minutes to test. There was a direct relationship between A5 FIBTEM and the rate of PPH progression to hemorrhages greater than 2500 ml in a study conducted by Kerry et al. [28]. It was proven in a study conducted by De Loyd et al. [29] that It is necessary to identify patients who need FC by ROTEM. Its routine administration is not recommended because the level of fibrinogen in mothers is physiologically higher than in the normal population. Even in most cases of PPH, this level is usually maintained higher than 200 mg/dl. An extensive study named "WOMAN" was conducted in the form of multicenter RCT in 2017. One of this study results was the emphasis on early treatment of mothers with PPH and has recommended the necessary treatments to be done during the first 3 hours after delivery. WOMAN study emphasizes rapid bedside monitoring of coagulation and early initiation of therapeutic interventions which is achieved by ROTEM [30]. Early treatment with FC and tranexamic acid has been emphasized in the study conducted by Gayet et al [31] expresses that every 15 minutes' treatment delay is associated with a 10% reduction in treatment efficacy, so told that treatment with tranexamic acid had no expected therapeutic effects after three hours of PPH initiation. These results have also been emphasized in the Crash clinical trial [32]. The treatment efficacy of recombinant factor VIIa in cases of severe PPH that did not respond to other treatments together with comorbidities such as hemophilia, congenital factor VIIa deficiency, inhibitor effect, congenital platelet dysfunction (Glanzmann thrombasthenia) has been evaluated in several studies, and despite the less agreeable therapeutic effects, the risk of thromboembolism has been increased by about 11% in some cases [33,34]. Hence, it is recommended to correct coexisting coagulopathic reasons that cause maternal hemorrhage, such as correction of anemia, electrolytes, acid-base disorders, hypothermia, etc. before deciding on the treatment with activated factor VIIa [35,36]. It should be regarded that no study has so far recommended applying PCC in mothers with hemorrhage, and the early treatment by the FC and TXA is emphasized [37]. Cryoprecipitate has a volume of 180 ml and contains 1.5 gr of fibrinogen per unit. One FFP unit has a volume of about 200 ml and on average includes 0.8 g of fibrinogen. One of the disadvantages of these products is the time-consuming process of cross-match, melting, and transferring the product, and also the probability of TACO while



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treating fibrinogen deficiency with FFP will be extremely higher than FC even in young and healthy mothers, according to the low 223 concentration of fibrinogen in FFP (consequently, FC seems to be a more reliable treatment 224 option) [38,39,40]. Lee et al. evaluated 132 Australian mothers who underwent cesarean delivery in 2019 by comparing their ROTEM outputs with the default values that have been provided by the device manufacturer and expressed different reference ranges [Table 1] [41].

Table 1: Comparison of baseline causes of infertility parameters between the type of ET

| ROTEM parameter | Normal range in term pregnancy |
|---|---|
| FIBTEM A5 | 13 – 28 mm |
| FIBTEM MCF | 16 – 34 mm |
| FIBTEM CT | 40 – 74 sec |
| EXTEM A5 | 39 – 66 mm |
| EXTEM CT | 43 – 69 sec |
| INTEM A5 | 38 – 63 mm |
| CT | < 100 sec |

## Conclusion

The main advantage of TEG/ROTEM is the possibility of performing a complete and real evaluation of homeostasis and help patient's individualized therapy using whole blood as a sample, which is the main aim of goal-directed therapy and is associated with the least complications and best outcomes [42]. Persistent PPH is usually triggered by the onset of coagulopathy (even before dilutional coagulopathy), and most routine coagulation tests (platelet, plasma fibrinogen level, PT, PTT, INR) are prepared at least after 60 minutes; consequently, it is quite common that the patient's coagulation status will change entirely at the time of receiving the results of these tests. Hence, a test with a rapid response at the patient's bedside is desired to collect accurate information about the patient's coagulation status. FIBTEM results can improve PPH management by two measures: primarily, as a predictor of severe PPH occurrence, and secondarily, as an early detection tool of coagulopathy. Consequently, FIBTEM ensures a brilliant future in the timely and optimal PPH crisis management. Parameters that are reported beforehand can help us promptly manage critical situations, including the α angle and A5 FIBTEM, which are ready in about 5 minutes, and studies have determined that they are completely related to more delayed parameters such as A10 and FIBTEM MCF, and hence, they are reliable for clinical judgment [43]. Studies have shown that preemptive treatments can highly prevent PPH's worsening from progression to DIC, which needs early and accurate knowledge of the patient's coagulation status. This is not possible with routine laboratory instruments due to the delay in their response and cannot be judged immediately and accurately based on the volume of bleeding and the patient's clinical examination because it gets too late to react. According to conducted studies, there is a strong direct relationship between parameters that are prepared very promptly (within 5 minutes), such as FIBTEM A5, α-FIBTEM, and laboratory fibrinogen level, and it has been confirmed that these parameters are incomplete correlation with FIBTEM MCF & EXTEM MCF. Therefore, they can be considered as a criterion for rapid therapeutic interventions. Preparing FIBTEM MCF takes 30-40 minutes and its normal range in the third trimester of pregnancy is 15-19 mm, while this range is 10-12 mm for the general population. Accordingly, the threshold for therapeutic intervention in mothers with PPH is completely different from other applications of ROTEM (such as cardiovascular surgery) and cannot be considered as similar approaches [44]. Studies suggest that in PPH cases we should credit the underlying etiology as a proven prognostic factor. For example, placental abruption with IUFD with any amount of bleeding is very dangerous and has a poor prognosis in the outcome. It has been recommended to perform early ROTEM testing and FC administration in cases where FIBTEM A5<12 mm. It is also important to pay attention to EXTEM CT, and coagulation factors must be administered in cases with CT above 100 seconds. After administering FC, by repeating the ROTEM in short time intervals, we get informed about the mother's new coagulation status and may repeat the treatment if necessary.

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