European Journal of Obstetrics & Gynecology and Reproductive Biology 223 (2018) 26–29

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Increased coagulation index as measured by Thromboelastography during ovarian stimulation for in vitro fertilization: Influence of the final oocyte maturation triggering agent

Ronit Beck-Fruchter[a,*], Israel Gavish[b], Shira Baram[a,c], Yoel Geslevich[a], Amir Weiss[a,c]

[a] Fertility and In-Vitro Fertilization Unit, Department of Obstetrics and Gynecology, Emek Medical Center, Afula, Israel
[b] Hematology Unit, Emek Medical Center, Afula, Israel
[c] Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ARTICLE INFO

Article history:
Received 31 October 2017
Received in revised form 6 January 2018
Accepted 7 February 2018
Available online xxx

Keywords:
Thromboelastogram
Ovarian hyperstimulation
Recombinant hCG
GnRH agonist
Coagulation

ABSTRACT

Objective: Thromboelastography (TEG) is a viscoelastic test of hemostasis which allows measurement of the processes of clot initiation, propagation, stabilization, and dissolution in real time. In this study we aimed to evaluate the alterations in coagulation as measured by TEG during In Vitro Fertilization (IVF) stimulation cycles and to investigate whether final oocyte maturation with recombinant hCG (rhCG) versus GnRH agonist results in a different coagulation state.

Study design: This is a prospective observational study which included fifty-three normogonadotrophic women. All the patients received an antagonist IVF treatment protocol. Final oocyte maturation was triggered with either rhCG (n = 25) or GnRH agonist (n = 26). Two patients did not complete the study due to poor response. Venous blood was drawn in the early and late follicular phase and on the day of ovum pickup. The TEG parameters assessed were R (time to first clot formation), K (time until the clot reaches a fixed strength), alpha angle (the rate of clot formation), MA (reflects maximum strength of the platelet-fibrin clot), LY30 (percent of clot lysis at 30 min after MA is reached) and the CI (the overall coagulability).

Results: The overall coagulation index of the entire study population was significantly increased on the day of ovum pickup as compared to the early follicular phase. This increase in the coagulation index was also significant in a subanalysis of patients triggered with rhCG. Contrarily, there was no significant increase in the coagulation index in the subgroup of patients triggered with GnRH agonist.

Conclusion: Our results demonstrate a procoagulable state in patients after ovulation induction. Final triggering with GnRH agonist rather than rhCG, might lower this hypercoagulability pattern.

Introduction

Infertility affects an estimated 80 million individuals worldwide, many of whom are treated with gonadotrophic hormones and assisted reproductive technology (ART) [1]. It is well known that ovarian stimulation procedures confer a risk of venous thromboembolism and an increased risk of arterial thrombosis also has been reported" [2]. The prothrombotic state is explained by alterations of both coagulation and fibrinolysis pathways [3], although the exact mechanism by which it is created has never been elucidated [4].

Thromboelastography (TEG) (TEGVR; Haemonetics,Braintree, MA) is a viscoelastic test of hemostasis in whole blood, which allows measurement of the processes of clot initiation, propagation, stabilization, and dissolution in real time. In addition, it is possible to separate the effects of platelets and fibrinogen on overall clot strength [5]. Initially, TEG has been used to guide transfusion strategy for bleeding patients, but recently it was demonstrated that TEG can also sensitively identify patients with a hypercoagulable state [6].

Only few studies have evaluated the alterations in coagulation and fibrinolysis as measured by TEG during ovarian stimulation. Harnett et al. reported that although significant changes were noted in both the clot formation time and the coagulation index, all TEG values remained within the normal range [7]. Recently, a significant difference was found in TEG parameters between the early and late follicular phase as well as between the early follicular

* Corresponding author.
E-mail address: r_beck@rambam.health.gov.il (R. Beck-Fruchter).

https://doi.org/10.1016/j.ejogrb.2018.02.005
0301-2115/

and late luteal phase of an IVF stimulation cycle, indicating a hypercoagulable state [8,9]. Additionally it was reported that TEG can be used to depict a hypercoagulable state in women with severe ovarian hyperstimulation syndrome (OHSS) [10].

The aim of this study was to evaluate the alterations in coagulation as measured by TEG during the early and late follicular phase and on the day of ovum pickup. Additionally, we aimed to investigate whether final oocyte maturation with either recombinant hCG (rhCG) or GnRH agonist results in a different coagulation state.

Materials and methods

Population

This was a prospective study which included normogonadotrophic women undergoing ART with an antagonist protocol. Patients were recruited prior to the treatment cycle. Each patient contributed only one cycle. Fifty-three patients were recruited.

Intervention

Gonadotropin stimulation was started on day three of the menstrual cycle. Stimulation doses were based on the patient's expected ovarian response according to prior treatments, age, weight, baseline follicle stimulating hormone (FSH) and antral follicle count. The choice of gonadotropin utilized varied and took into account the patient's preference, insurance coverage, cost and compliance. GnRH antagonists were administered when the leading follicle reached 14 mm and were continued daily up to oocyte maturation triggering. The antagonist used was either Cetrorelix (as acetate) 0.25 mg (Cetrotide, Merck Serono S.A., Switzerland) or Ganirelix 0.25 mg (Orgalutran, N.V. Organon, Netherlands). Patients were monitored for follicle growth and endometrial thickness. Ovulation trigger was administered when at least three follicles reached 17 mm. Patients were triggered either using 0.2 mg triptorelin acetate (Decapeptyl, Ferring Pharmaceuticals Israel) or by Choriogonadotropin alfa (250 mcg, Ovitrelle, Serono S.A.). Oocyte pickup (OPU) was scheduled 35–37 h after the trigger.

Outcome measure

Venous blood for estrogen and progesterone levels as well as clot kinetics was drawn within the first three days of the cycle prior to treatment with gonadotropins (early follicular phase), on the day of ovulation triggering or one day before (late follicular phase) and on the day of ovum pickup.

The TEG variables collected from each sample included:

The reaction time R (time to first clot formation), clotting time K (the time until a 20 mm amplitude is achieved on the graph), alpha angle (the rate of clot formation), the maximum amplitude MA (reflects maximum strength of the platelet-fibrin clot), LY30 (percent of clot lysis at 30 min after MA is reached) and the overall coagulation index (CI) which represents the overall coagulability.

Statistical analyses

The statistical analyses and data management were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was determined if $P < 0.05$. Continuous variables were presented with mean ± standard deviation (for parametric analyses) or median and interquartile range (for non-parametric analyses). Each marker was measured 3 times. The change (difference) was calculated by subtracting the marker's value at each pair time points (1–2, 1–3 and –3, overall three change variables). The difference in TEG variables between the three phases (i.e. early follicular phase, late follicular phase and ovum pickup day) were analyzed with the non-parametric Friedman test for repeated measures. Pairwise comparisons were performed using Wilcoxon sign-rank test with Bonferroni correction. The differences in outcome measures at TEG 3 between women who received GnRH agonist and those who received rhCG were analyzed with the Wilcoxon two sample test. The association between estradiol levels, the age of the patient and TEG parameters was estimated using the Spearman correlation.

Ethical approval

The study was approved by the local ethical committee. Using GnRH agonist for final oocyte maturation in normal responders was registered in the clinical trial protocol registration system (NCT01638026). A signed written informed consent was obtained from all participants in the study.

Results

Fifty-three patients were enrolled. The ovum pick up was cancelled in two patients due to low ovarian response. Ovulation induction was achieved with rhCG in 25 patients and with GnRH agonist in 26. Basic characteristics of the investigated subjects are presented in Table 1. No significant differences regarding these basic characteristics were found between the rhCG and the GnRH agonist groups.

Complete TEG parameters at all the three time points were available for 38 patients.

Estradiol and progesterone levels, as well as TEG values during the early and late follicular phase and on the day of ovum pickup are listed in Table 2. Most of the TEG measurements were within normal range (Table 2). The time interval from the beginning of the test until initial fibrin formation (R) and until the clot reached a fixed strength (K) were significantly shorter on the day of ovum pickup as compared to the early follicular phase ($P = 0.001$, $P = 0.02$), and the overall coagulation index (CI) was significantly higher ($P = 0.0003$). The differences in R and CI were also significant when comparing the day of ovum pickup with the late follicular phase ($P = 0.0027$, $P = 0.015$).

In patients who were administered rhCG for final oocyte maturation, R was significantly shorter ($P = 0.005$) and CI was significantly increased ($P = 0.0018$) at the ovum pickup day as compared to the early follicular phase. These changes reflecting a shift towards a procoagulative state were not significant in the GnRH agonist group. Despite this, a significant increase in the maximal strength of the platelet-fibrin clot (as reflected by the MA) was observed in this group on the day of ovum pickup.

R on the day of ovum pickup was significantly shorter in the rhCG triggered group as compared to the GnRH agonist triggered group ($P = 0.04$) (Table 3).

Table 1
Demographic, baseline and stimulation data.

Variable	Study population	hCG trigger	GnRHa trigger
Patients, (n)	51	25	26
Age (y)	29.6 ± 5.4	29.7 ± 5.1	29.4 ± 5.7
Body mass index (Kg)	25.6 ± 5.9	26.2 ± 6.5	25.2 ± 5.4
Basal FSH (IU/L)	7.3 ± 2.8	7.47 ± 3.2	7.2 ± 2.3
Infertility duration (y)	2.8 ± 1.9	2.4 ± 1.6	3.2 ± 2.1
Total dose of FSH (IU)	1843.1 ± 1143.8	1884 ± 1481.7	1803.8 ± 711
Maximal E_2* (pg/ml)	1404.3 ± 742.8	1267.8 ± 738	1535.6 ± 737.6
Oocytes aspirated (n)	9.9 ± 6.8	8.1 ± 5.7	11.8 ± 7.4

Data presented as mean ± SD.
* E_2 – Estradiol.