



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

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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.

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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).

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 Cetrotrel (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 $\pm$ 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	GnRH trigger
Patients, (n)	51	25	26
Age (y)	29.6 $\pm$ 5.4	29.7 $\pm$ 5.1	29.4 $\pm$ 5.7
Body mass index (Kg)	25.6 $\pm$ 5.9	26.2 $\pm$ 6.5	25.2 $\pm$ 5.4
Basal FSH (IU/L)	7.3 $\pm$ 2.8	7.47 $\pm$ 3.2	7.2 $\pm$ 2.3
Infertility duration (y)	2.8 $\pm$ 1.9	2.4 $\pm$ 1.6	3.2 $\pm$ 2.1
Total dose of FSH (IU)	1843.1 $\pm$ 1143.8	1884 $\pm$ 1481.7	1803.8 $\pm$ 711
Maximal E ₂ (pg/ml)	1404.3 $\pm$ 742.8	1267.8 $\pm$ 738	1535.6 $\pm$ 737.6
Oocytes aspirated (n)	9.9 $\pm$ 6.8	8.1 $\pm$ 5.7	11.8 $\pm$ 7.4

Data presented as mean $\pm$ SD.

* E₂ – Estradiol.

Table 2

Serum hormones levels and TEG parameters during IVF treatment.

	Early follicular phase	Late follicular phase	Ovum pickup day	Normal range
Patients, (n)	51	43	43	
E ₂ (pg/ml)	61.6 ± 93 ^{a,b}	1404.3 ± 742.8 ^c	960.6 ± 500	
Progesterone (ng/ml)	0.7 ± 0.3 ^{a,b}	0.9 ± 0.4 ^c	4.9 ± 3	
R (minutes)	5.3 (4.6–6.3) ^a	5.2 (4.7–6) ^c	4.6 (3.7–5.2)	4–8
K (minutes)	1.2 (1.1–1.6) ^a	1.2 (1–1.6)	1.2 (0.9–1.4)	1–4
Alpha angle (degree)	70.2 (66.7–73.1)	71.4 (66.2–74.8)	71.4 (67.5–75.2)	47–74
MA (mm)	68.5 (64.9–73)	69.3 (66.9–73.4)	70.1 (67.5–74)	55–73
LY30 (%)	0.6 (0.2–2.2)	0.7 (0.2–1.8)	0.7 (0.3–1.6)	0–8
CI (AU)	2 (0.9–2.9) ^a	2.4 (0.9–2.8) ^c	2.8 (1.7–3.8)	–3–3

Data presented as mean ± standard deviation for parametric tests and median (interquartile range) for non-parametric tests.

^a Significant difference between late and early follicular phase.^b Significant difference between ovum pickup day and early follicular phase.^c Significant difference between ovum pickup day and late follicular phase.**Table 3**

TEG parameters at ovum pick up (TEG 3) and the differences between the early follicular phase (TEG 1) and these parameters, presented independently according to the trigger agent.

	hCG				GnRH agonist			
	Early follicular phase	Ovum pickup day	The dynamic between TEG1 & TEG3	P	Early follicular phase	Ovum pickup day	The dynamic between TEG1 & TEG3	P
R (minutes)	5.45 (4.6–6.3)	4 (3.7–4.8) [*]	1.3 (0.5–1.9)	0.005	5.3 (4.7–6.5)	4.9 (4.3–5.2) [*]	0.5 (–0.45–1.55)	NS
K (minutes)	1.2 (1.05–1.4)	1.15 (0.8–1.4)	0.1 (0–0.3)	NS	1.4 (1.2–1.6)	1.2 (1–1.5)	0.1 (0–0.3)	NS
Alpha angle (degree)	72 (66.05–73.45)	70.2 (67–76.2)	–0.1 (–4.4–3.4)	NS	69.7 (67–72)	71.9 (68.3–74.9)	–1.3 (–5.35–3.1)	NS
MA (mm)	71 (65.8–73.8)	70.55 (68.9–74.8)	–0.3 (–2.7–1.9)	NS	67.8 (63.5–69.1)	69.8 (66.7–72.8)	–1.75 (–4.15–0.2)	0.015
LY30 (%)	0.55 (0–1.95)	0.75 (0.4–1.2)	–0.1 (–1.1–0.8)	NS	0.6 (0.3–2.5)	0.7 (0.2–2)	0.1 (–0.5–0.85)	NS
CI (AU)	2.3 (0.65–3)	2.9 (2.1–3.8)	–0.95 (–1.7–0.05)	0.0018	1.6 (0.9–2.6)	2.7 (1.5–3.4)	–0.65 (–1.5–0.4)	NS

Data presented as median (interquartile range).

For each measure, the difference between TEG1 and TEG3 was calculated. Wilcoxon sign-rank test was used to examine the significance of the difference.

^{*} Significant statistical difference in R time at ovum pickup day between hCG and GnRH agonist triggered patients (P < 0.05).

No correlation was found between the estradiol levels or the patient's age and the TEG parameters.

Comment

This study investigated the TEG changes occurring during the IVF cycle. The coagulation parameters were obtained at three-time points: at the beginning of the cycle (lowest levels of estradiol), around ovulation triggering (maximal estradiol levels) and on the day of ovum pickup. Additionally, we inquired whether a difference in coagulation exists between patients who were triggered with rhCG versus those who received GnRH agonist.

The association between hormonal stimulation and thromboembolic disorders is well known. Women conceiving through IVF have a 10 times higher risk for venous thromboembolism (VTE) during the first trimester compared with women conceiving spontaneously [11]. Previous studies demonstrate that ovarian stimulation may induce a procoagulable state due to an increase in coagulation factors and a reduction in anticoagulation factors [11–14]. The increased coagulation factors include vonWillebrand factor, factor VIII, factor V and fibrinogen and the reduced anticoagulation factors including antithrombin, protein C and protein S. The clot formation time and platelet function are unchanged according to other studies [4]. Most of the reported changes are modest and remain within the normal range [4,11].

Our findings demonstrate that as compared to the early follicular phase, after ovulation triggering there is an increase in coagulation parameters. These changes in coagulation are reflected

by a significant reduction in the time R, an indicator of faster clot formation and in the time K, an indicator of faster polymerization. In addition, a highly statistically significant increase in the CI, represents increased overall coagulability. Increased coagulation was also demonstrated when comparing the late follicular phase with the ovum pickup day, although only R and CI reached statistical significance.

Three previous studies used TEG to evaluate the coagulation process during in vitro fertilization. Harnett et al. found that R was significantly shorter and CI was significantly increased at oocyte retrieval when compared with baseline [7]. Orbach-Zinger compared values between the early and late follicular phase and found differences in all the parameters reflecting clot formation (R, K, Angle, MA, and CI) but not clot lysis (LY 30) [8]. Cohen et al. found a significant increase only in CI before ovulation triggering, while 2 weeks after the ovum pick up a significant difference was demonstrated also in R, K, Alpha and MA (but not in LY30) [9]. The same group also demonstrated alterations in all clot formation parameters in patients who developed ovarian hyperstimulation syndrome [10].

In our study, no correlation was found between the estradiol levels and the TEG parameters. The time of maximal procoagulative state according to the TEG parameters was on the day of ovum pickup, and not on the day of maximal estradiol levels. Although Orbach-zinger did report a correlation between estradiol and TEG parameters, Cohen et al. failed to demonstrate such a connection. On the contrary, the maximal CI was measured 2 weeks after the ovum pick up, while estradiol levels were at their

nadir [8,9]. Other researchers also didn't find a correlation between fibrinogen levels and estrogen concentrations during IVF cycle and concluded that at E2 peak, there is no significant modification of hemostasis activation markers [12]. A study investigating thrombin generation and hemostatic parameters during a natural menstrual cycle found that thrombin generation is significantly higher during the luteal phase compared with the follicular phase and concluded that it was the progesterone and not the estradiol that had the greatest influence on hemostasis [15].

The known association between elevated estrogen concentrations and thromboembolic complications led researchers to assume that the supra-physiological levels of estrogens exert direct effects on hemostatic variables and induce a procoagulable state [11]. Despite this, most ART related thromboembolic complications do not occur at the time of peak estradiol levels but 10–40 days later [4]. The lag between the time of estradiol peak and the time of thromboembolic complications can imply that additional factors may play a role in the pathogenesis of thromboembolism in women undergoing ovarian stimulation. Since ovarian hyperstimulation syndrome and pregnancy are major risk factors for thromboembolic complications, it was suggested that hCG may have a role in the procoagulant state in these women [9]. OHSS rarely develops without exposure to hCG, either exogenous as an ovulation trigger, luteal phase support or endogenous production from the trophoblast in pregnancy. Moreover, the elevated hCG rise accompanying multiple pregnancies can aggravate already existing OHSS [16]. The connection to thromboembolic complication was also implied in cases of recurrent thromboembolism in a male patient treated with hCG for hypogonadism and as a complication of the “hCG diet” [17,18]. Avoiding hCG is a known strategy to avoid OHSS (and hence reduce the risk for thromboembolic complication) [19–21]. In the current study we demonstrated that in patients who were exposed to hCG, the time until initial fibrin formation was significantly shorter than in patient who were triggered with GnRH agonist. However, a significant increase in the maximal strength of the platelet-fibrin clot was found after GnRH agonist triggering. A connection between GnRH and platelets has already been described. It was suggested that GnRH by way of its effect on the hypophysis and ovary, enhance platelet-activating factor [22]. Since MA reflects mostly thrombocyte function, this might explain its significant increase after GnRH agonist trigger. Nonetheless, we found a significant increase in the coagulation index after rhCG triggering while after GnRH agonist triggering this was not the case. As coagulation index represents the overall coagulability, this strengthens the hypothesis that hCG may have a significant role in the procoagulative state.

In conclusions TEG parameters suggest a procoagulable state in patients after ovulation induction. We report for the first time, that final triggering with GnRH agonist rather than rhCG, might lower this hypercoagulability pattern. The exact mechanisms and the clinical manifestation are yet to be investigated.

References

- [1] Luke B. Pregnancy and birth outcomes in couples with infertility with and without assisted reproductive technology: with an emphasis on US population-based studies. *Am J Obstet Gynecol* 2017;217(September (3)):270–81, doi: <http://dx.doi.org/10.1016/j.ajog.2017.03.012> [Internet] Elsevier Inc. Available from.
- [2] Grandone E, Villani M. Assisted reproductive technologies and thrombosis. *Thromb Res* 2015;135(S1):S44–45, doi: [http://dx.doi.org/10.1016/S0049-3848\(15\)50441-6](http://dx.doi.org/10.1016/S0049-3848(15)50441-6) [Internet] Elsevier Masson SAS Available from.
- [3] Sticchi E, Romagnuolo I, Cellai AP, Lami D, Fedi S, Prisco D, et al. Fibrinolysis alterations in infertile women during controlled ovarian stimulation: influence of BMI and genetic components. *Thromb Res* 2012;130(6):919–24, doi: <http://dx.doi.org/10.1016/j.thromres.2012.07.005> [Internet] Elsevier Ltd. Available from.
- [4] Chan WS. The ART of thrombosis: a review of arterial and venous thrombosis in assisted reproductive technology. *Curr Opin Obstet Gynecol* 1927;2017–18, doi: <http://dx.doi.org/10.1097/GCO.0b013e328329c2b8> [Internet] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19276806> 5Cn.
- [5] Whiting D, Dinardo JA. TEG and ROTEM: technology and clinical applications. *Am J Hematol* 2014;89(2):228–32.
- [6] Park MS, Martini WZ, Dubick MA, Salinas J, Butenas S, Kheirabadi BS, et al. Thromboelastography as a better indicator of postinjury hypercoagulable state than prothrombin time or activated partial thromboplastin time. *J Trauma* 2009;67(2):266–76.
- [7] Harnett MJP, Bhavani-Shankar K, Datta S, Tsen LC. In vitro fertilization-induced alterations in coagulation and fibrinolysis as measured by thromboelastography. *Anesth Analg* 2002;95(4):1063–6 table of contents.
- [8] Orbach-Zinger S, Eidelman LA, Lutsker A, Oron G, Fisch B, Ben-Haroush A. The effect of in vitro fertilization on coagulation parameters as measured by thromboelastogram. *Eur J Obstet Gynecol Reprod Biol* 2016;201:118–20, doi: <http://dx.doi.org/10.1016/j.ejogrb.2016.04.010> [Internet]. Elsevier Ireland Ltd. Available from.
- [9] Cohen Y, Tulandi T, Almog B, Zohav E, Deutsch V, Many A, et al. Prolonged activation of the coagulation system during in vitro fertilization cycles. *Eur J Obstet Gynecol Reprod Biol* 2017;216:111–5, doi: <http://dx.doi.org/10.1016/j.ejogrb.2017.07.021> [Internet] Elsevier Ireland Ltd Available from.
- [10] Zohav E, Almog B, Cohen A, Levin I, Deutsch V, Many A, et al. A new perspective on the risk of hypercoagulopathy in ovarian hyperstimulation syndrome using thromboelastography. *Reprod Sci* 2017, doi: <http://dx.doi.org/10.1177/1933719117697257> [Internet] 1933719117697257 Available from.
- [11] Eichinger S, Evers JH, Glasier A, La Vecchia C, Martinelli I, Skouby S, et al. Venous thromboembolism in women: a specific reproductive health risk. *Hum Reprod Update* 2013;19(5):471–82.
- [12] Biron C, Galtier-Dereure F, Rabesandratana H, Bernard I, Aguilar-Martinez P, Schved JF, et al. Hemostasis parameters during ovarian stimulation for in vitro fertilization: results of a prospective study. *Fertil Steril* 1997;104–9 [Internet] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8986692>.
- [13] Westerlund E, Henriksson P, Wallén H, Hovatta O, Wallberg KR, Antovic A. Detection of a procoagulable state during controlled ovarian hyperstimulation for in vitro fertilization with global assays of haemostasis. *Thromb Res* 2012;130(4):649–53, doi: <http://dx.doi.org/10.1016/j.thromres.2011.11.024> [Internet] Elsevier Ltd Available from.
- [14] Jozwik M. The mechanism of thromboembolism in the course of ovarian hyperstimulation syndrome. *Med Wieku Rozwoj* 2012;16(4):269–71.
- [15] Chaireti R, Gustafsson KM, Byström B, Bremme K, Lindahl TL. Endogenous thrombin potential is higher during the luteal phase than during the follicular phase of a normal menstrual cycle. *Hum Reprod* 2013;28(7):1846–52 [Internet] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23592222>.
- [16] Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2017(1) 2017.
- [17] Goodbar NH, Foushee JA, Eagerton DH, Haynes KB, Johnson AA. Effect of the human chorionic gonadotropin diet on patient outcomes. *Ann Pharmacother* 2013;47(5).
- [18] Glueck CJ, Lee K, Prince M, Jetty V, Shah P, Wang P. CORRIGENDUM to four thrombotic events over 5 years, two pulmonary emboli and two deep venous thrombosis, when testosterone-HCG therapy was continued despite concurrent anticoagulation in a 55-Year-Old man with lupus anticoagulant. *J Investig Med High Impact Case Reports* 2017(1), doi: <http://dx.doi.org/10.1177/2324709616689401> 5Cn [Internet] 2324709616689401 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28321420> 5Cn <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5347271>.
- [19] Kol S, Humaidan P. GnRH agonist triggering: recent developments. *Reprod Biomed Online* 2013;226–30.
- [20] Pfeifer S, Butts S, Dumesic D, Fossum G, Gracia C, La Barbera A, et al. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertil Steril* 2016;106(7):1634–47.
- [21] Youssef Mohamed AFM, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Lib* 2014.
- [22] Bódis J, Papp S, Vermes I, Sulyok E, Tamás P, Farkas B, et al. Platelet-associated regulatory system (PARS) with particular reference to female reproduction. *J Ovarian Res* [Internet] 2014;7:55 Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4039651&tool=pmcentrez&rendertype=abstract>.