Ovarian stimulation for IVF and fibrin clot phenotype

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INTRODUCTION

Controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF) is a routine procedure in infertility treatment. Despite the transfer of good-quality embryos, only 30-40% of cycles result in clinical pregnancy (3). It is suggested that unfavorably altered coagulation and fibrinolysis processes may also be responsible for IVF failures (4,5). IVF-induced supraphysiological estrogen levels may lead to deterioration of embryo implantation and placental blood circulation and, therefore, decrease pregnancy outcomes (6). This study purpose was to investigate the impact of both protocols long GnRH-agonist (GnRH-a) and GnRH-antagonist (GnRH-ant) on fibrin clot properties together with thrombin generation and fibrinolysis. Assessments of plasma fibrin clot permeability (K_s), efficiency of fibrinolysis using clot lysis time (CLT), along with thrombin generation (prothrombin fragments 1+2 [F1+2] and endogenous thrombin potential [ETP]) and fibrinolysis inhibitors were performed together with clinical pregnancy rate.

RESULTS

The study included 129 women. There were no differences in AMH levels, mean serum FSH, the duration of stimulation, and total recombinant FSH doses and pregnancy outcomes between both groups. Despite comparable estradiol levels before and after COH between both protocols, we showed 12% higher mean change in estradiol level (p=0.04) in GnRH-ant group compared to GnRH-a women (data not shown).

The GnRH-ant protocol resulted in increased ETP (+9.8%; Fig.1, panel C) along with slightly reduced K_s (-2.4%; Fig.2, panel C) with no influence on CLT (Fig.3, panel C).

COH with the GnRH-a protocol reduced thrombin generation by decreasing both ETP (-6.6%; Fig.1, panel D) and F1+2 (-30.8%; data not shown) and favorably altered fibrin clot properties represented by increased K_s (+21.7%; Fig.2, panel D) and reduced CLT (-13.8%; Fig. 3, panel D) as well as decreased PAI-1 levels (by 2.5-times, data not shown).

The GnRH-ant compared to the GnRH-a protocol increased PAI-1 levels (+77.3%; data not shown), thrombin generation (9.3% higher ETP; Fig.1, panel B), and K_s (+13.7%; Fig.2, panel B). After COH, women from the GnRH-a protocol had more compact fibrin clot structure confirmed by SEM analysis (Fig. 4A) compared to those from the GnRH-ant group (Fig. 4B)

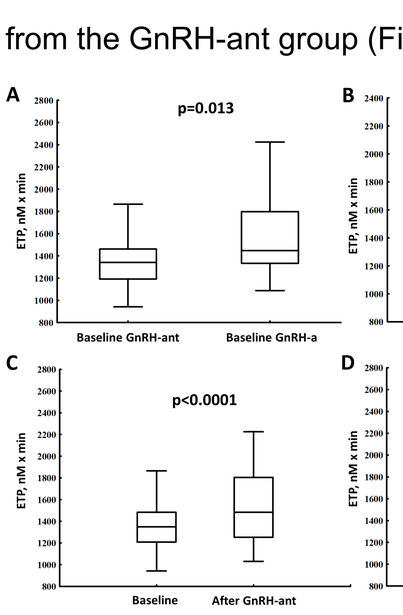

Figure 1. Endogenous thrombin potential (ETP). At baseline (panel A), after controlled ovarian hyperstimulation (COH; panel B), in women from gonadotropin-releasing hormon antagonist (GnRH-ant; panel C) and GnRH agonist (GnRH-a; panel D).

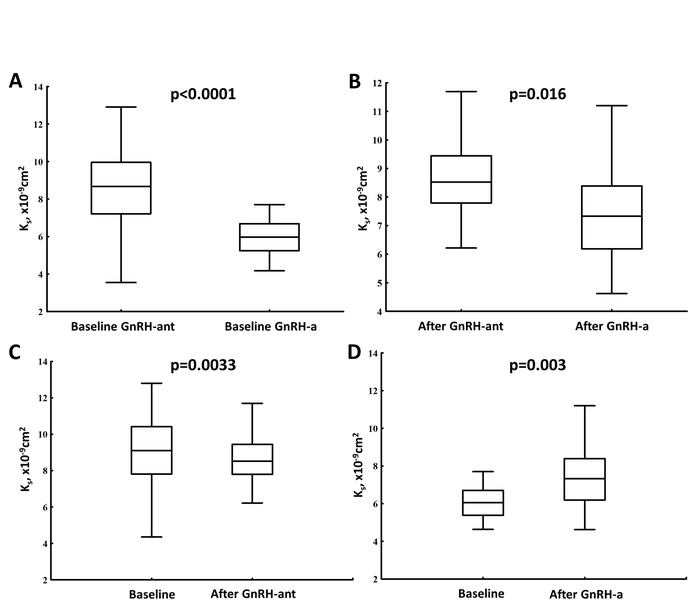

Figure 2. Fibrin clot permeability (K_s). At baseline (panel A), after controlled ovarian hyperstimulation (COH; panel B), in women from gonadotropin-releasing hormon antagonist (GnRH-ant; panel C) and GnRH agonist (GnRH-a; panel D).

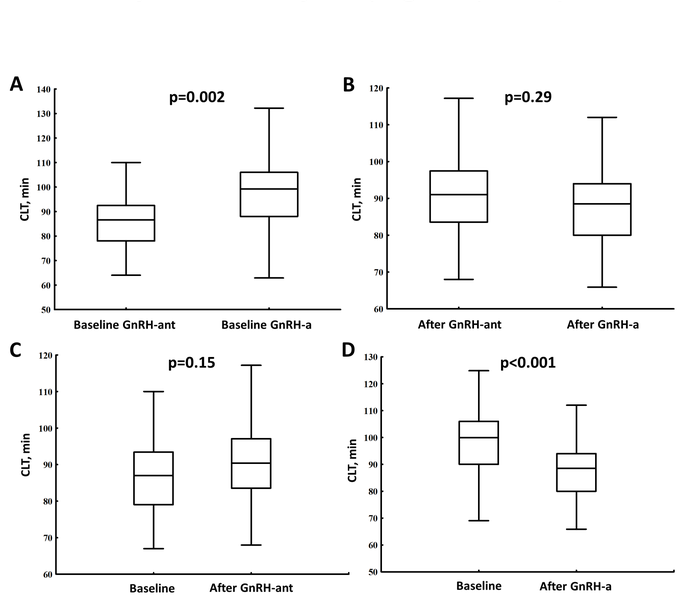

Figure 3. Clot lysis time (CLT). At baseline (panel A), after controlled ovarian hyperstimulation (COH; panel B), in women from gonadotropin-releasing hormon antagonist (GnRH-ant; panel C) and GnRH agonist (GnRH-a; panel D).

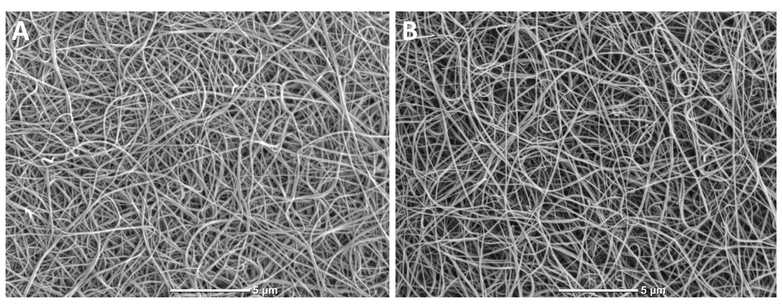

Figure 4. Representative scanning electron micrographs showing morphology of fibrin clots prepared from plasma of women treated with the GnRH-a protocol (panel A) or using the GnRH-ant (panel B). Scale bar, 5 µm, magnification 5000x.

CONCLUSION

The GnRH-ant protocol enhanced thrombin generation and slightly decreased fibrin clot density. COH with the GnRH-a reduced thrombin generation and favorably changed fibrin clot features. Improvement of fibrin clot permeability, at least in part might be associated with positive pregnancy outcome.

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