Correlation assessment between the time of trigger administration and embryological results

Shurygina Oksana [1,2] Yukhimets Sergei[3], Tugushev Marat[1,2], Shipulin Nikita[4]

[1]Department of Reproductive Medicine, Clinical Embryology and Genetics, Samara State Medical University, Ministry of Health of Russian Federation, [2]Medical Company IDK", GC "Mother and Child" (Samara), [3] Department of Morphology and Pathology, Medical University "Reaviz“ , Department of Obstetrics and Gynecology, Bashkir State Medical University Ministry of Health of the Russian Federation[4]

Abstract

The oocytes final maturation trigger is usually prescribed 35-37 hours before oocytes retrieval, however, this is still a controversial clinical issue, as there is not enough data especially for recombinant-hCG (r-hCG) trigger.

Analysis of embryological results with stratification by the trigger exposure , the age of the patient and the predicted ovarian response can be a tool for determining the best time for oocytes retrieval

Contact Information

Oksana Viktorovna Shurygina
Email: oks-shurygina@yandex.ru
Website: https://samara.mamadeti.ru
Phone:+79608101000

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Introduction

The modern practice of assisted reproductive technologies (ART) is based on a personalized approach within the framework of approved clinical guidelines, which optimizes the procedures' effectiveness and safety. The use of the final oocytes maturation trigger is widely described in the literature as a key injection of the controlled ovarian stimulation cycle. In routine clinical practice, the trigger is usually prescribed 35-37 hours before oocytes retrieval. However, the exposure time of the trigger is still a controversial clinical issue, as there is not enough data on its specificity for a human Chorionic Gonadotropin (hCG) drugs, in particular the r-hCG trigger. This study aimed to conduct a retrospective comparative analysis of oocytes and embryological parameters at different time intervals of r-hCG exposure from the moment of drug injection to oocyte retrieval in patients with different profiles and ages: in groups 18-34 years, 35-40 years; in groups of predicted poor, normal and hyper ovarian response.

Methods and Materials

This retrospective cohort single-center study included 959 patients (IVF/ICSI) aged 18 to 40 years who received r-hCG (Ovitrelle®, 6500 IU 250 µg / 0.5 ml, Merck Serono, Italy) as a trigger of final oocytes maturation. GnRH antagonists and GnRH agonists protocols were used for the controlled ovarian stimulation and various gonadotropins: rFSH, hMG, rLH, and their combinations. The assessment was stratified by the exposure time after administration of r-hCG: 35 hours, 36 hours and 37 hours; as well as in groups 35 hours / 36 and more hours. The statistical analysis was carried out considering the patients' different clinical profiles and ages: in the predicted poor / normal / hyper ovarian response groups (PR, NR, HR) and the age groups of 18-34 and 35-40.

Primary endpoints: the proportion of mature oocytes at metaphase II stage (MII) and the proportion of patients with MII> 80%. **Secondary endpoints**: proportion of oocytes recovered (OO), normal fertilization rate, cleavage rate, blastocyst development rate (BR) (good blastocyst development rate on Day 5). The embryos were cultured under conditions of low oxygen concentration in COOK incubators using sequential media (G-1^{TM}PLUS, G-2^{TM} PLUS, Vitrolife, Sweden). Statistical analysis was performed using RStudio (R v.3.6.3, RStudio v.1.1.463). The sample size calculation was based on a pilot study and calculated using the formula for the proportion test; level p <.05 was considered statistically reliable and is specified for the comparison groups in which it was achieved.

Results

On average, the MII rate in the study population was 79%, the BR was 53%. The MII in all time interval was not below the threshold levels, specified in the Vienna Consensus 2017: mean MII rate at 35 hours was 76.4, 95% CI (73.18, 79.55); at 36 hours – 79.7, 95% CI (78.3, 81.1); at 37 hours – 79.4, 95% CI (74.4, 84.3). The proportion of patients with MII>80% in the population was comparable in time intervals at 35 hours - 54.6, 95% CI (47.2, 61.9) and 36 hours or more - 57.5, 95% CI (54.0, 60.9). In the subgroup analysis patients with predicted hyper ovarian response in the study population MII rate at 35 vs. 36 hours was 57.1, 95% CI (44.7, 69.6) vs. 75.5, 95% CI (70.8, 80.3), *p=0.0133*. As for the blastocyst development rate in the subgroup of 35 years and older the difference was at 35 hours - 43.3, 95% CI (36.5, 50.1) vs. 36 hours - 52.7, 95% CI (48.8, 56.7), *p=0.0388.*

Table 1.

	OO	MII	BR	
35 hours	80,1	76,4	50,2	NS
36 hours	79,3	79,7	54,3	NS
37 hours	76,6	79,4	45,2	NS
PR	79,8	84,7	60,8	NS
NR	79,7	80	52,6	NS
HR	78,1	71,3	52,6	NS
<35 years	79,2	78,2	54.3	NS
≥35 years	80	80,5	50.5	NS

Discussion

In our routine clinical practice, stimulation protocols with r-hCG demonstrated high performance in key embryological indicators, that were not below the threshold levels specified in the Vienna Consensus of 2017. Even though in this study the proportion of MII oocytes and the proportion of patients with MII>80% were comparable in the time intervals of 35, 36 and 37 hours, attention was drawn to the fact that in subgroups analysis the best results in patients with predicted hyper ovarian response were obtained with a longer exposure interval. This finding is probably due to a more prolonged maturation phase of the nuclear and oocyte cytoplasm in hyper responders because of the large number of growing follicles. Another possible correlating factor in predicted hyper responders was a significantly lower total dose of FSH per cycle in our study. As for the blastocyst development rate in the study population, the clinically meaningful difference was revealed with the highest rates at 36 hours (in the subgroup of 35 years and older that difference reached p<0.05)

Conclusions

Final oocytes maturation in ART is a complex process influenced by various factors, in particular the trigger of oocyte maturation. In our study, 36 hours exposure interval of the r-HCG trigger corresponds to the clinically highest levels of oocytes recovered, mature oocytes and blastocyst development rate. An algorithm was proposed and tested for analyzing data on the embryological effectiveness of the r-hCG trigger, which was based on the time interval of exposure, the age of the patient and the predicted ovarian response.

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