

GYNECOLOGY

Effect of letrozole on moderate and severe early-onset ovarian hyperstimulation syndrome in high-risk women: a prospective randomized trial



Qingyun Mai, MD, PhD¹; Xiaokun Hu, MD¹; Gang Yang, MD; Yingyi Luo, MD; Kejun Huang, MD; Yuan Yuan, MD; Canquan Zhou, MD

BACKGROUND: Ovarian hyperstimulation syndrome is an iatrogenic complication of controlled ovarian stimulation. Early ovarian hyperstimulation syndrome occurs during luteal phase of controlled ovarian stimulation within 9 days after human chorionic gonadotropin trigger and reflects an acute consequence of this hormone on the ovaries. Late ovarian hyperstimulation syndrome occurs 10 or more days after human chorionic gonadotropin trigger and reflects increased endogenous human chorionic gonadotropin levels following pregnancy. Human chorionic gonadotropin stimulates granulosa-lutein cells to produce vascular endothelial growth factor messenger RNAs, which in turn raises serum vascular endothelial growth factor concentration and increases vascular permeability in women with ovarian hyperstimulation syndrome. Efforts to reduce the incidence and severity of ovarian hyperstimulation syndrome after oocyte retrieval, and in particular primary prevention efforts, are vital to prevent thrombogenesis and other serious complications.

OBJECTIVE: The objective of the study was to compare the efficacy of letrozole, an aromatase inhibitor, with aspirin in primary prevention of early ovarian hyperstimulation syndrome and to compare vascular endothelial growth factor levels between groups.

STUDY DESIGN: Participants in this prospective randomized trial included 238 participants undergoing cryopreservation of the whole embryos after oocyte retrieval with at least 1 of the following high-risk factors for ovarian hyperstimulation syndrome: oocyte retrieval ≥ 25 ; estradiol level ≥ 5000 pg/mL on the day of human chorionic gonadotropin administration; and clinical or ultrasonographic evidence of ovarian hyperstimulation syndrome on the day of oocyte retrieval, such as ultrasonographic evidence of ascites. After human chorionic gonadotropin triggering, experimental (119 cases) and control (119 cases) groups

received letrozole and aspirin, respectively, for 5 days. The 5 categories of ovarian hyperstimulation syndrome include no, yes-mild, yes-moderate, yes-severe, and yes-critical. The primary outcome was the incidence and severity of early ovarian hyperstimulation syndrome. The secondary outcome included vascular endothelial growth factor level both on the second and seventh day after the human chorionic gonadotropin trigger, and clinical and laboratory features of ovarian hyperstimulation syndrome symptoms.

RESULTS: The incidence of ovarian hyperstimulation syndrome was significantly higher in women receiving aspirin, compared with letrozole (90.2% vs 80.4%, $P = .044$). Moderate and severe ovarian hyperstimulation syndrome was also higher in the aspirin group, 45.1%, compared with the letrozole group, 25.0% ($P = .002$). Moreover, the duration of luteal phase was shortened in letrozole group compared with aspirin group (8.1 ± 1.1 days vs 10.5 ± 1.9 days, $P < .001$). The vascular endothelial growth factor level was significantly higher in the letrozole-treated group than aspirin-treated group (0.49 ± 0.26 vs 0.42 ± 0.22 , $P = .029$).

CONCLUSION: Letrozole was more effective than aspirin in decreasing the incidence of moderate and severe early-onset ovarian hyperstimulation syndrome. Our results indicate that ovarian hyperstimulation syndrome might be caused through a luteolytic effect rather than through modulation of vascular endothelial growth factor, racing by a decline in estradiol and termination of early-onset ovarian hyperstimulation syndrome in advance in high-risk women with cryopreservation of the whole embryos.

Key words: aspirin, in vitro fertilization, letrozole, ovarian hyperstimulation syndrome, vascular endothelial growth factor

Ovarian hyperstimulation syndrome, an iatrogenic complication of controlled ovarian stimulation occurring during luteal phase or early pregnancy, is exclusively associated with an exaggerated ovarian response to exogenous gonadotropin stimulation.

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The incidence of moderate to severe ovarian hyperstimulation syndrome is 3.1–8.0% for in vitro fertilization cycles but can reach to 20.0% for high risk women.¹

The disease severity of ovarian hyperstimulation syndrome can be classified as mild, moderate, severe, and critical according to clinical manifestations and laboratory findings.² Compared with the patients with mild ovarian hyperstimulation syndrome, more organs are affected in the severe and critical subsets.

Lyons et al³ were the first to describe 2 distinct patterns of ovarian

hyperstimulation syndrome: the early and late forms. Early ovarian hyperstimulation syndrome occurs in the luteal phase of controlled ovarian stimulation within 9 days after human chorionic gonadotropin trigger and reflects an acute consequence of exogenous human chorionic gonadotropin on ovaries. On the other hand, late ovarian hyperstimulation syndrome occurs 10 days after a human chorionic gonadotropin trigger and is the consequence of an increase of endogenous human chorionic gonadotropin levels following pregnancy.

Ovarian hyperstimulation syndrome prevention is a multistage

TABLE 1
Classification of OHSS severity^a

OHSS stage	Clinical features	Laboratory features
Mild	Abdominal bloating/discomfort	No important laboratory alterations
	Mild nausea/vomiting	
	Diarrhea	
	Enlarged ovaries	
Moderate	Mild features +	Elevated hematocrit (>41%)
	Ultrasonographic evidence of ascites	Elevated WBC (>15*10 ⁹ /L)
		Hypoproteinemia
Severe	Mild and moderate features +	Hemoconcentration (hematocrit >55%)
	Clinical evidence of ascites	WBC >25*10 ⁹ /L
	Hydrothorax	Creatinine clearance <50 mL/min
	Severe dyspnea	Creatinine >115 μmol/L
	Oliguria/anuria	Na+ <135 mmol/L
	Intractable nausea/vomiting	K+ >5.0 mmol/L
	Tense ascites	Elevated liver enzymes
	Low blood/central venous pressure	
	Rapid weight gain (>1 kg in 24 h)	
	Syncope	
	Severe abdominal pain	
	Venous thrombosis	
Critical	Anuria/acute renal failure	Worsening of findings
	Arrhythmia	
	Thromboembolism	
	Pericardial effusion	
	Large pleural effusion	
	Arterial thrombosis	
	Adult respiratory distress syndrome	

OHSS, ovarian hyperstimulation syndrome; WBC, white blood cell count.

^a Data from Navot et al.²Mai et al. Letrozole decreases incidence of early-onset OHSS. *Am J Obstet Gynecol* 2017.

the ovarian stimulation protocol appropriately.⁴

Secondary prevention, on the other hand, is extended to patients who have mounted an exaggerated response to controlled ovarian stimulation and aims to prevent progression to ovarian hyperstimulation syndrome, for example, through cryopreservation of embryos. However, even with embryo cryopreservation, patients are still exposed to exogenous human chorionic gonadotropin, and early ovarian hyperstimulation syndrome cannot be avoided completely.

Although human chorionic gonadotropin has no direct vasoactive properties,⁵ it stimulates granulosa-lutein cells to produce vascular endothelial growth factor/vascular endothelial growth factor receptor-2 messenger RNAs, which in turn raises serum vascular endothelial growth factor concentration and increases vascular permeability in ovarian hyperstimulation syndrome.⁶ Soares et al⁷ pointed out that expression of vascular endothelial growth factor/vascular endothelial growth factor receptor-2 messenger RNAs correlates with enhanced vascular permeability, and both peak at 48 hours after human chorionic gonadotropin injection.

Recently the administration of letrozole during the luteal phase of in vitro fertilization cycles offers another therapeutic modality for patients at high risk of ovarian hyperstimulation syndrome because letrozole drastically reduces estradiol levels by blocking human aromatase in a potent, specific, and reversible way. Indeed, 2 randomized controlled trials that evaluated administration of letrozole during luteal phase in in vitro fertilization cycles concluded that letrozole drastically decreased estradiol concentration,^{8,9} preventing ovarian hyperstimulation syndrome.

In this regard, letrozole may offer a promising selection for patients at high risk for ovarian hyperstimulation syndrome who cryopreserve their embryos aiming to reduce the potential risk that high estradiol concentrations pose.^{10,11}

It has been known that vascular endothelial growth factor is the major mediator of ovarian hyperstimulation

process and can be classified into 2 main categories: primary and secondary. The key step of primary ovarian hyperstimulation syndrome prevention is to recognize the preexisting risk factors and individualize

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