Granulocyte colony-stimulating factor as a potential inducer of ovulation in infertile women with luteinized unruptured follicle syndrome

TAKEO SHIBATA, SATORU MAKINODA, TOMOO WASEDA, HIDEKI TOMIZAWA, RYOTA FUJII, and TAKAFUMI UTSUNOMIYA

UCHINADA AND OITA, JAPAN

Luteinized unruptured follicle (LUF) syndrome is one of the intractable ovulation disorders that are commonly observed during cycles of treatment with ovulation inducers, for which no effective therapy other than assisted reproductive technology is available. Here, we investigated whether granulocyte colony-stimulating factor (G-CSF) could prevent the onset of LUF syndrome. We analyzed the effects of G-CSF in 68 infertile women with LUF syndrome who received ovulation induction (clomiphene + human chorionic gonadotropin (hCG) therapy or follicle-stimulating hormone + hCG therapy). G-CSF (lenograstim, 100 μg) was administered subcutaneously. Onsets of LUF syndrome were compared between the cycle during which G-CSF was given in combination with the ovulation inducer (ie, the G-CSF treatment cycle) and the subsequent cycle during which only the ovulation inducer was given (ie, the G-CSF nontreatment control cycle). The results showed that LUF syndrome recurred in only 3 cycles during the G-CSF treatment cycle (4.4% (3/68 cycles)), whereas LUF syndrome recurred in 13 cycles during the subsequent G-CSF nontreatment control cycle (19.1% (13/68 cycles)). The additional use of G-CSF significantly prevented the onset of LUF syndrome during ovulation induction ($P = 0.013$, McNemar test). No serious adverse reactions because of the administration of G-CSF were observed. In conclusion, our findings indicate that G-CSF may become a useful therapy for LUF syndrome. (Translational Research 2016;171:63–70)

Abbreviations: ART = assisted reproductive technology; FSH = follicle-stimulating hormone; G-CSF = granulocyte colony-stimulating factor; hCG = human chorionic gonadotropin; LUF = luteinized unruptured follicle; NSAIDs = nonsteroidal anti-inflammatory drugs; WBC = white blood cell

From the Department of Obstetrics and Gynecology, Kanazawa Medical University, Uchinada, Japan; St. Luke Clinic, Oita, Japan.

This article was presented at the International Federation of Fertility Societies (IFFS) International Symposium, Yokohama, Japan on April 26, 2015.

Submitted for publication May 5, 2015; revision submitted September 18, 2015; accepted for publication October 8, 2015.

Reprint requests: Takeo Shibata, Department of Obstetrics and Gynecology, Kanazawa Medical University, Uchinada 920-0293, Japan; e-mail: ma30408@kanazawa-med.ac.jp.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.10.003

INTRODUCTION

Ovulation disorders are one of the major causes of female infertility.[1] The selective estrogen receptor modulator (clomiphene) or gonadotropins (ie, follicle-stimulating hormone [FSH] and human chorionic gonadotropin [hCG]) are widely used for the treatment of ovulation disorders. Clomiphene is known to induce ovulation fairly well,[2] whereas adverse effects of clomiphene lead to cervical mucus insufficiency,[3] thinning of the endometrium,[4] and luteinized unruptured follicle (LUF) syndrome.[5]

AT A GLANCE COMMENTARY

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Background

As a part of cancer chemotherapy, granulocyte colony-stimulating factor (G-CSF) has been used for at least 30 years in clinical practice for the treatment of neutropenia. No serious adverse drug reactions have been reported with the use of G-CSF, to the best of our knowledge.

Translational Significance

The present study clinically demonstrated that G-CSF is useful for infertile women diagnosed with luteinized unruptured follicle caused by ovulation induction.

LUF syndrome is an intractable ovulation disorder in which the luteinization of ovarian follicles is observed without follicle rupture or ovum extrusion.[5] Although the cause of LUF syndrome is still unknown, groups have suggested that endometriosis[6,7] or the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during the periovulatory phase[8] could cause LUF syndrome. Because NSAIDs inhibit not only the production of prostaglandin but also neutrophil chemotaxis,[9,10] reduced inflammatory reactions because of NSAID use during ovulation could contribute to the onset of LUF syndrome.

A well-known hypothesis proposed by Espey[11] in 1980 focused mainly on the mechanism of ovulation as an inflammatory reaction. Neutrophils, which play a central role in inflammatory reactions, infiltrate the thecal layer during the periovulatory phase of the menstrual cycle.[12] Granulocyte colony-stimulating factor (G-CSF) is generally known as a cytokine that induces inflammatory reactions, thereby enhancing neutrophil function, and G-CSF and its receptor are known to be produced by granulosa cells.[13] We reported that the G-CSF messenger RNA levels in granulosa or theca cells were increased by at least 10-fold during the preovulatory late follicular phase compared with other phases of the menstrual cycle,[14] suggesting an important role for G-CSF in the mechanism of ovulation during the late follicular phase.

In the field of cancer chemotherapy, recombinant human G-CSF has been used for at least 30 years in clinical practice for the treatment of neutropenia. No serious adverse drug reactions have been linked to the use of G-CSF, to the best of our knowledge. Under these circumstances, we conducted the present study to evaluate whether the administration of an inducer of inflammatory reaction, G-CSF, would be feasible as a treatment for LUF syndrome.

METHODS

Patients. Infertile women who had been diagnosed with LUF syndrome at least once participated in the present clinical study. The inclusion criteria were as follows: age <40 years and no severe pelvic adhesions around the ovaries and fallopian tubes as assessed by laparoscopy. The exclusion criteria were as follows: (1) white blood cell (WBC) count ≥10,000/μL at the time of the administration of G-CSF; (2) severe disorders of the liver, kidney, or heart; (3) allergic predisposition; and (4) any other conditions assessed by the investigator as leading to the patient being ineligible for participation in the study. To evaluate the effects of the additional use of G-CSF on LUF syndrome, we compared the number of cycles showing a recurrence of LUF syndrome between the cycle during which G-CSF was given in combination with ovulation inducers (clomiphene + hCG therapy or FSH + hCG therapy; ie, the G-CSF treatment cycle) and the subsequent cycle during which only prescribed therapy was given (ie, the G-CSF nontreatment control cycle). The type, dose, and duration of each ovulation inducer were tightly equalized between the G-CSF treatment cycle and the G-CSF nontreatment control cycle.

The present study was conducted at the Department of Obstetrics and Gynecology of Kanazawa Medical University and at St. Luke Clinic from April 2006 to March 2015. Because patients with relatively uncommon LUF syndrome were enrolled in the study, the study required a longer period of time; however, the same evaluation methods were used throughout the study. Written informed consent was obtained from all study patients before the administration of G-CSF. The study was conducted after being approved by the Ethics Review Board of Kanazawa Medical University (Number 90).

Criteria for ovulation and LUF syndrome. We monitored the patients' follicular development by transvaginal ultrasonography and with measurements of their serum estradiol levels. Both ovulation and LUF syndrome were diagnosed using serial transvaginal ultrasonography in the period between the follicular and luteal phases (Fig 1). Ovulation was diagnosed if any of the following 4 criteria were met after the hCG administration: (1) reduction in the mean diameter of dominant follicles, indicating the process of follicular rupture[15]; (2) disappearance of the dominant follicles, indicating the complete rupture of follicles; (3) morphologic changes within the dominant follicles, indicating the