PMDA Alert for Proper Use of Drugs
Pharmaceuticals and Medical Devices Agency
No. 14 April 2022

Ovarian Hyperstimulation Syndrome Caused by Drugs Used for Treatment of Infertility

Ovarian hyperstimulation syndrome (OHSS) is known to be an adverse reaction to drugs used for ovulation induction or controlled ovarian stimulation in infertility treatment, and precautions have been issued in the package insert, etc.

There has been an increasing trend in the number of adverse drug reaction reports and payments/non-payments in the Relief System for Adverse Drug Reactions (hereinafter referred to as “the Relief System”) concerning OHSS in recent years (see [Reference] on page 2). Cases have been confirmed where treatment such as controlled ovarian stimulation is continued while observing symptoms corresponding to moderate OHSS.

When using these drugs, please pay sufficient attention to the following points by carefully reading the package insert for each drug, or Indications, Dosage and Administration, and Precautions to be added[*2], which are shown in the Notifications on Off-label Use of Drugs Evaluated in Advance for Public Knowledge-based Application[*1] so that OHSS is detected early and appropriate measures are taken.

◎Please explain to patients about ovarian hyperstimulation syndrome.

- **Ovarian hyperstimulation syndrome may occur. Symptoms to be noted.**
- **Patients should immediately consult their physicians, etc. when any abnormalities are observed.**

◎Please pay attention to the following points. If ovarian hyperstimulation syndrome is observed, take appropriate measures such as discontinuation of administration.

- **Patient's subjective symptoms (severe pelvic pain, lower abdominal pain, tense feeling of lower abdomen, low back pain, nausea/vomiting, etc.)**
- **Rapid weight gain**
- **Ovarian enlargement (pelvic examination, ultrasonography, serum estradiol level test, etc.)**

*1 "Off-label Use of Drugs Newly Evaluated in Advance for Public Knowledge-based Application by the Pharmaceutical Affairs and Food Sanitation Council" (PSEHB/PED Notification No. 0128-1/PSEHB/PSD Notification No. 0128-1 dated January 28, 2022, and PSEHB/PED Notification No. 0225-2/PSEHB/PSD Notification No. 0225-1 dated February 25, 2022 [Correction, March 14, 2022])

*2 Regarding the contents shown in the Notifications, each marketing authorization holder makes a partial change application, and the package insert will be revised after the approval. Please check the latest package insert thereafter.

Summary of typical cases in which continuation of infertility treatments resulted in severe OHSS.

- A case receiving controlled ovarian stimulation using human menopausal gonadotrophin (hMG). The ovaries were found to be considerably enlarged due to a large number of developing follicles and the serum estradiol (E_2) level exceeded 20 000 pg/mL; development of moderate OHSS was considered, however, human chorionic gonadotrophin (hCG) was administered on the same day. At least 40 eggs were retrieved and OHSS became severe on the day of egg retrieval. The patient was admitted to the hospital for treatment.
- A case of polycystic ovarian syndrome receiving controlled ovarian stimulation with hMG. During administration of hMG, the serum E_2 level was 10 000 pg/mL or higher, the maximum diameter of the ovary exceeded 8 cm, and ascites was observed. Although it is considered that moderate OHSS developed, hMG and hCG were administered on the same day. Immediately after the egg retrieval, OHSS became severe, which required admission and intensive care.
- A case receiving controlled ovarian stimulation using hMG and purified human menopausal gonadotrophin (uFSH). The serum E_2 level before egg retrieval was 10 000 pg/mL or higher, the maximum diameter of the ovary exceeded 8 cm, and ascites was observed. Although it is considered that moderate OHSS developed, hCG was administered on the same day. Immediately after retrieval of 60 or more eggs, the patient was admitted to the hospital for severe OHSS.

[Reference]

■ **The number of adverse drug reactions of OHSS reported to PMDA and the number of payments/non-payments in the Relief System in PMDA for relief of adverse drug reactions between FY2017 and FY2021**

	2017	2018	2019	2020	2021
Number of reports of adverse drug reactions*	70	58	59	72	81
Number of payments/non-payments in the Relief System	12	9	23	46	51
Of these, number of non-payments	0	0	1	2	4

* Total number of adverse drug reactions reported to PMDA as an adverse drug reaction term “ovarian hyperstimulation syndrome” by marketing authorization holders or medical professionals from April 2017 to March 2022. (as of March 31, 2022)

■ **Adverse drug reactions by hMG, hCG, choriogonadotropin alfa (genetical recombination), follitropin alfa (genetical recombination), or uFSH have been frequently reported among the reported adverse drug reactions and cases judged for relief in FY2021.**

About this information

- PMDA Alert for Proper Use of Drugs communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among Adverse Drug Reaction/infection cases reported in accordance with the PMD Act.
- We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future
- This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibility on them, but is provided to promote the proper use of the drugs.

Access to the most up to date safety information is available via the PMDA medi-navi.

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