Annual report of Reproductive Endocrinology Committee, Japan Society of Obstetrics and Gynecology, 2019

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Abstract

The Japan Society of Obstetrics and Gynecology Reproductive Endocrinology Committee summarizes the activities of each subcommittee below from April 2017 to March 2019.
1. Current important issues regarding reproductive medicine were examined and discussed from social, political, ethical and scientific viewpoints.
2. A nation-wide survey targeted at OB/GYN facilities revealed the usual procedure in diagnosis and management of fertility-desiring POI patients and fertility outcomes of the patients.
3. How to introduce and adapt FIGO AUB systems to obstetric and gynecologic practices in Japan was examined and discussed.

Key words: ART, atypical uterine bleeding, menstrual disorder, primary ovarian insufficiency, risk management.

Annual report of reproductive medicine risk management subcommittee in 2018

Minoru Irahara, Yukiko Katagiri, Hidekazu Saito, Yasushi Takai, Kenichi Tatsumi, Toshio Hamatani, Toshihiro Fujiwara, Akira Kasahara

Introduction

We held a subcommittee twice

1. The first: July 12, 2018 in Tokyo Station Conference
2. The second: January 16, 2018 in Tokyo Station Conference

Conclusion

1. Correspondence to the Japan Society of Reproductive Medicine (JSRM) “Guidelines for Freezing and Preservation of Unfertilized Eggs and Ovarian Tissues.” Regarding the “Guidelines on freezing and preservation of unfertilized ova and ovary tissue” published on March 30, 2019 by JSRM, we examined the correspondence as Japan Society of Obstetrics and Gynecology (JSOG) and there is no conflict with JSOG various guidelines. It was confirmed.
2. About development of guidelines about research using genome editing technology to human fertilized embryo which Ministry of Health, Labor and Welfare, Ministry of Education, Culture, Sports, Science and Technology advances to:
The Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science and Technology promoted the development of guidelines on the use of embryos for genome editing technology, and confirmed that there were no problems as a whole.

3. About the problem of preservation system of preserved embryos and gametes.
As it became clear that the preservation state of embryos stored at member institutions was bad, we decided to call out to all members using Home Page and our academic journals.

4. About handling of frozen embryo after closure of ART registration facilities.
Regarding the handling of frozen embryos after closing if the ART facility is closed for any reason, after closing the ART registration facility as defined by the Ethics Committee (Registration and Survey Subcommittee). We examined the contents of the By-Laws regarding registration refusal caused by etc. and confirmed that we will continue to comply in accordance with these by-laws.

5. Examination of the current state of Artificial Insemination with Donor (AID) in Japan.
The current status of AID in Japan was analyzed, and it was found that there was a decrease in sperm providers to AID for various reasons, and that commercial-based sperm banks, etc. wanted to enter, etc. It was recognized that there is a need to consider.

Survey of diagnosis and management of patients with primary ovarian insufficiency and desired fertility

Tetsuo Maruyama, Sayaka Uchida, Akira Iwase, Kazuhiro Kawamura, Hideya Sakakibara, Toshifumi Takahashi, Yukihiro Terada

Introduction
Due to the recent trend of late marriage and childbirth in Japan, primary ovarian insufficiency (POI)/premature ovarian failure/premature menopause has emerged as a cause for infertility among women of reproductive age. Many treatment protocols for follicular development and ovulation induction have been tested in women with POI and desired fertility; however, none have approached the success rate of utilizing donor oocytes. Thus, for couples affected by POI, the most practical alternatives for having a child are adoption or oocyte donation, both of which have limited availability in Japan. Most Japanese patients with POI and desired fertility therefore choose infertility treatments with unproven efficacy. We distributed a mailed and web-based survey consisting of two sequential questionnaires aimed at understanding the usual procedure in diagnosis and management of POI patients with desired fertility by obstetricians and gynecologists, and the statistics pertaining to POI patients across Japan.

Materials, methods and results
We sent a primary questionnaire by mail in August 2018 to each of 5261 OB/GYN clinics and hospitals registered in the Japan Association of Obstetricians and Gynecologists (JAOG). The questionnaire consisted of four questions to determine the number of patients with POI for the past 3 years and whether or not the POI patients with desired infertility can be treated. Based on the results of the primary questionnaire, we selected medical facilities where POI patients with desired fertility were diagnosed and treated. In October 2018, we asked each of the selected facilities via mail to respond to a web-based secondary questionnaire. The secondary questionnaire consisted of 14 questions to determine the facility outline, the number of POI patients, especially patients with desired fertility for the past 5 years, diagnostic and therapeutic infertility treatment modalities for POI, and the treatment outcomes. In both primary and secondary questionnaires, we provided general information as a reference on how to diagnose POI. Indeed, the diagnostic criteria for POI varied among facilities.

Results and discussion
Among the 5261 medical facilities, 2958 facilities responded to the primary questionnaire. Among the 790 facilities selected on the basis of the primary survey, 331 responded to the secondary questionnaire. One hundred sixty-seven of the 331 facilities were capable of diagnosing and treating patients with POI and desired fertility, whereas the remaining 164 facilities were capable of diagnosing POI, but referred patients with POI and desired fertility to more specialized facilities. One hundred twenty-one of the 167 self-contained medical facilities (72.5%) had one or more board-certified reproductive medicine specialists, and 148 of the 167 facilities (88.6%) were registered by the Japan Society of Obstetrics &
Diagnosis of POI
The 331 respondents were permitted to make multiple selections on the secondary questionnaire from a list of examinations for the diagnosis and treatment of POI, and the percentage of respondents who selected the corresponding item were as follows: measurement of circulating FSH and LH levels (98.8%); measurement of circulating estradiol levels (98.8%); antral follicle count (AFC) by ultrasound (90.9%); thyroid function testing (88.8%); measurement of circulating anti-Müllerian hormone (AMH) level (63.7%); measurement of circulating autoantibodies (42.6%); karyotyping (38.1%); measurement of bone mineral density (29.9%); and measurement of circulating inhibin B levels (1.5%). No respondents chose ovarian biopsy.

In response to the question which asked what are the four most important examinations and information for the diagnosis of POI, the 331 respondents selected the circulating FSH level (99.7%), the circulating estradiol level (90.3%), the duration of amenorrhea (82.4%), the circulating AMH level (63.0%) and the AFC (57.9%).

Infertility treatment of patients with POI and desired fertility
The 167 facilities capable of diagnosing and treating patients with POI and desired fertility were asked on the secondary questionnaire to select the first-line treatment for follicular development and ovulation induction. Ninety-nine (59.3%) of the 167 facilities selected cyclic estrogen in combination with progestin therapy as first-line treatment. Subsequently, 14.4%, 13.2%, and 9.0% of the 167 respondents selected clomiphene, estrogen in combination with urinary/recombinant FSH, and urinary/recombinant FSH alone.

To achieve pregnancy, 77 (46.1%) of 167 facilities instructed the POI patients to have timed intercourse, whereas 73 (43.7%) facilities recommended IVF/ICSI. Several major facilities where infertility treatment utilizing in vitro activation of dormant ovarian follicles was available did not respond to this survey.

Treatment outcome
The responding facilities had 2055 POI patients in the past 5 years. Of these 2055 POI patients, 1165 (56.6%) had follicular development on at least one occasion. Two hundred eighty-six patients (13.9%) conceived with their own oocytes and 180 (8.8%) had live births. Although these treatment outcomes should be interpreted with caution, this nationwide survey targeted OB/GYN facilities for the first time and revealed the usual procedures undertaken in the diagnosis and management of patients with POI and desired fertility by

It remains unclear which therapeutic modalities resulted in pregnancies. As mentioned in the limitation of this survey section, we should be cautious regarding the interpretation of treatment outcomes.

Limitation of this survey
This survey targeted medical facilities rather than individual physicians. Therefore, the results of this survey did not precisely reflect the decision-making process of individual physicians in the diagnosis and treatment of POI. Because this survey was not an individual case study, the data on the number of POI patients and the treatment outcomes might have been based on the memories of respondent physicians rather than the clinical records in some cases. We did not provide strict diagnostic criteria for POI or enrollment criteria in this survey, raising the possibility that poor ovarian responders and patients with decreased ovarian reserve might have been included in this survey. Several high volume and specialized centers, presumably with a substantial number of POI patients, did not respond to the secondary questionnaires. Therefore, the results did not precisely reflect the current status of POI management across Japan due to the exclusion of POI patients.

Despite these limitations, this survey covered OB/GYN facilities as much as possible across Japan. It is likely that POI patients are diagnosed, managed and followed, not only by primary clinics, but also by tertiary medical facilities, including university hospitals. In the light of the study focus and scale, this is the first nationwide survey involving the treatment of patients with POI and desired fertility in Japan.

Conclusions
Approximately 60% of 167 facilities treated POI patients with cyclic estrogen and progestin therapy as a so-called expectant management, but once follicular development occurred, approximately 44% of the 167 facilities recommended ART to actively attempt pregnancy. For the past 5 years, approximately 50% of 2055 POI patients presented features indicating follicle growth on at least one occasion. Two hundred eighty-six patients (13.9%) conceived with their own oocytes and 180 (8.8%) had live births. Although these treatment outcomes should be interpreted with caution, this nationwide survey targeted OB/GYN facilities for the first time and revealed the usual procedures undertaken in the diagnosis and management of patients with POI and desired fertility by

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obstetricians and gynecologists with the relevant statistics across Japan.

Disclosure

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported. The Jumbo Co., Ltd. and Rakuten Insight Inc. assisted in the administration of the questionnaires, but had no role in the analysis and interpretation of the data.

Standardization of diagnoses for menstrual disorders

Akira Iwase, Yasushi Takai, Hiroshi Ishikawa, Osamu Yoshino, Koji Kugu

Introduction

Menstrual disorders including abnormal uterine bleeding (AUB) are some of the most common health issues faced by women of reproductive age. A wide range of investigations for menstrual disorders have been published. However, one major issue is that terminology used to describe menstrual disorders are not uniformly defined. Therefore, the International Federation of Gynecology and Obstetrics (FIGO) developed the universal systems of nomenclature and classification of AUB in 2011. The systems called FIGO AUB System 1 and 2 (also known as the PALM-COEIN System [for polyps, adenomyosis, leiomyoma, malignancy and hyperplasia-coagulopathy, ovulatory disorders, endometrial causes, iatrogenic and not classified]) have been revised in 2018 and are now widely used. On the other hand, the nomenclature and definitions of AUB in Japan have not been revised since 1990. This situation can be problematic in international collaborative research and it can impact evidence-based clinical

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<th>FIGO</th>
<th>JSOG</th>
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<tbody>
<tr>
<td>frequent</td>
<td>normal</td>
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<tr>
<td>-23 days</td>
<td>24–38 days</td>
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<td>oligomenorrhea</td>
<td>amenorrhea</td>
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<td>frequent</td>
<td>normal</td>
</tr>
<tr>
<td>-6 days</td>
<td>normal or regular</td>
</tr>
<tr>
<td>-7 or 9 days</td>
<td>8 or 10 days–irregular menstruation</td>
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| -9 days [18-25 y.o.], -7 days [26-41 y.o.], -9 days [42-43 y.o.]

<table>
<thead>
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<th>FIGO</th>
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<tr>
<td>frequency</td>
<td>normal</td>
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<tr>
<td>20* mL</td>
<td>20-140* mL</td>
</tr>
<tr>
<td>hypomenorrhea</td>
<td>hypermenorrhea or menorrhagia</td>
</tr>
<tr>
<td>patient determined</td>
<td>patient determined</td>
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*no definition for the menstruation with shortened duration

Figure 1 Comparisons of the definitions of AUB. The terms that FIGO does not recommend using anymore are shown in parentheses. JSOG, Japan Society of Obstetrics and Gynecology; FIGO, International Federation of Gynecology and Obstetrics.

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implications. The Japan Society of Obstetrics and Gynecology (JSOG) Reproductive Endocrinology Committee recognizes the necessity for the revision of the nomenclature and definitions of AUB in Japan.

Methods
The JSOG Reproductive Endocrinology Committee organized the subcommittee for the standardization of diagnoses for menstrual disorders with five clinician-investigators. Diagnoses and treatments for menstrual disorders have been discussed in the guidelines committee. Therefore, the subcommittee for the standardization of diagnosis for menstrual disorders focuses more on the nomenclature and definitions of AUB and on a possible field survey regarding the current management of AUB in Japan.

Results
Figure 1 shows the comparison of the definitions of AUB between the FIGO System 1 and JSOG. The JSOG definitions are mainly based on data from the studies in the 1950s and 1960s. In the FIGO systems, some terms such as hypermenorrhea are not recommended for use anymore. Some Japanese terminology corresponding to these terms are still very commonly used by clinicians.

Future activities
There are several differences in the definition of menstrual disorders between the FIGO systems and JSOG. The JSOG definitions are based on relatively old data. Therefore, the JSOG definitions should be revised according to the FIGO standards. It would be necessary and helpful to have comments and input from JSOG members before revisions are developed and issued. The committee discusses Japanese terminology corresponding to the terms FIGO abandoned as well as the necessity of a field survey on the current situation regarding AUB in Japan.

Acknowledgments
This study was approved and fully supported by the JSOG and JAOG. We would like to express our sincere gratitude to the JSOG, JAOG and all the physicians who honorably responded to our questionnaires.

Disclosure
None declared.