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Review

Regenerative medicine in Obstetrics & Gynecology: Current status under the Act on the Safety of Regenerative Medicine in Japan

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ABSTRACT

Introduction: While the provision of unapproved regenerative medicine has been problematic worldwide, few studies have examined the implementation status of regenerative medicine (RM) in the specific field. This study aimed to determine the current status of therapy and clinical research in the obstetrics and gynecology (OBGYN) in Japan under the Act on the Safety of Regenerative Medicine (RM Act).

Methods: Detailed data were extracted from publicly available websites provided by the Ministry of Health, Labour, and Welfare. We extracted descriptive details, including risk classification of the RM Act, modality, target disease, locality, institution, and administration route. For therapy, the price for each modality was evaluated.

Results: The total number of therapeutic provision plans in OBGYN (1.9% of RM in Japan) are classified as Class II (moderate) risk. Most were administered in clinics in urban areas for treating endometrial or ovarian infertility by locally administering platelet-rich plasma (PRP) or autologous mesenchymal stem cells (MSCs). The price using MSCs is approximately eight times more expensive that of those involving PRP (1832.1 ± 1139.8 vs 240.8 ± 106.5 thousand yen, $p < 0.0001$). Regarding research, four plans (2.2%) were submitted to target implantation failure and advanced gynecological cancer using autologous lymphocytes, dendritic cells, or MSCs.

Conclusion: The RM Act permits knowledge of the current status of regenerative medicine even for unapproved uses in a specific clinical field. The study findings shall prompt a worldwide discussion regarding the required regulations for therapy and clinical research of RM.

Contents

Abbreviations: RM Act, the Act on the Safety of Regenerative Medicine; RM, regenerative medicine; CP products, cell processing products; PMD Act, the Pharmaceuticals and Medical Devices Act; MHLW, the Ministry of Health, Labour, and Welfare; OBGYN, obstetrics and gynecology; PRP, platelet-rich plasma; MSC, mesenchymal stem cells; CAR-T, chimeric antigen receptor-T; jRCT, the Japan Registry of Clinical Trials; CGT products, cell and gene therapy products; SD, standard deviation; ADSCs, adipose tissue-derived stem cells; MenSCs, menstrual blood-derived stem cells.

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1. Introduction

In Japan, the Act on the Safety of Regenerative Medicine (RM Act) was implemented on November 25th, 2014. The RM Act stipulates regulations that doctors, certified committees, and cell processing facilities must adhere to when administering regenerative medicine (RM) in therapy mainly including private practice and clinical research for the efficient implementation of safe RM [1]. Under the RM Act, all RM provision plans involving therapy and clinical research using cell processing products (CP products), except for clinical trials under the Pharmaceuticals and Medical Devices Act (PMD Act) for pharmaceutical approval, must be reviewed by certified committees, which are certified by the Minister of Health, Labour, and Welfare, and subsequently submitted to the Minister [2]. The RM Act classified RM into three categories according to potential risk. Class I is RM with high risk using pluripotent stem, allogenic, transfected, or animal cells. Class II is associated with moderate risk and mainly includes autologous mesenchymal stem cells or somatic cells not for homologous use. Class III is considered to have low risk and includes autologous somatic cells for homologous use [1].

While it has been considered problematic worldwide that unapproved RMs are provided to patients and there has been no regulation regarding RM in the other countries [3,4]. On the other hand, in Japan, the detailed content of individual provision plans is also publicly available on the websites provided by the Ministry of Health, Labour, and Welfare (MHLW) under the RM Act. Thus, the RM Act permits knowledge of the current status of RM even for unapproved uses [5].

Recently, the development of RM has emerged in the field of obstetrics and gynecology (OBGYN), both in Japan and other countries [6–11]. For example, in the field of infertility treatment, platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) have been used for the treatment of infertility caused by injured endometrium and ovarian insufficiency [12,13]. Furthermore, autologous immune cell-based therapy and ex vivo gene therapy using chimeric antigen receptor-T (CAR-T) cells are also expected to be used for advanced or refractory gynecologic cancers [14]. However, contrary to these expectations, RM provision plans primarily involve orthopedics, dentistry and cosmetic use, whereas those in the OBGYN field were minor in Japan [15]. In addition, details of the Japanese status of RM in this field are not well understood. For example, which modality is primarily used, what diseases are targeted, what provision plans are available, and the price in private practice?

In this study, we comprehensively examined publicly available databases for RM to determine the current status of therapy and clinical research of RM in the field of OBGYN in Japan.

2. Materials and methods

2.1. Study design and data collection

Data were extracted from publicly available information registered on the e-Regenerative Medicine (https://saiseiiryo.mhlw.go.jp/) for therapeutic provision plans and the Japan Registry of Clinical Trials (jRCT) (https://jrct.niph.go.jp/) for research provision plans at the end of December 2023. Both websites were provided by the MHLW. From the titles of all RM provision plans, those targeting OBGYN diseases were eligible. In contrast, therapies involving cell and gene therapy products (CGT products) with pharmaceutical approval and clinical trials for pharmaceutical approval as CGT products under the PMD Act are not covered by the RM Act and were not included in this study. For therapeutic provision plans, detailed data were primarily extracted from the informed consent forms or records of committee meetings listed in the e-Regenerative Medicine. For unavailable cases, the data were supplemented from the websites of hospitals or clinics. Data that could not be extracted from any official materials were considered missing values. For research provision plans, detailed data were collected from the jRCT. The two websites, e-Regenerative Medicine and jRCT, have been publicly accessible since January 2019. The precise approval date of the provision plan starting before 2018 was not available; thus, these plans were analyzed together as pre-2018 plans.

2.2. Outcomes and variables

Our primary interests included descriptive epidemiologic data regarding provision plans for RM therapy and clinical research in the OBGYN field. Specifically, we included risk classification of the provision plan, characteristics of the region and implementing medical institution, modality of the CP products, targeted disease, and administration route. Regional characteristics were examined by dividing the population of each prefecture into two groups: those with over 3 million people and those with under 3 million people. The characteristics of the implementing medical institutions were classified based on whether they were hospitals with 20 or more beds or other clinics. The annual number of modalities and targeted diseases in the submitted plans were also examined descriptively. For our secondary interest, the price per modality was statistically analyzed in the therapeutic provision plans. For PRP, the price per treatment cycle was analyzed, and for MSC, the price per administration with the minimum number of transplanted cells was also analyzed. For research provision plans, we collected clinical research-specific information, such as study

design, study phase, primary outcomes, and recruitment status at the time of the study.

2.3. Statistical analysis

Continuous data are presented as the mean ± standard deviation (SD) and analyzed using a Student's t-test or one-way ANOVA test. Categorical data are presented as percentages and analyzed using a Chi-square test. Prism 9.4.0 software (Graph-Pad, Inc.) was used for statistical analyses. $P < 0.05$ was considered statistically significant.

2.4. Ethical statement

Because we used only publicly available information, we did not require any research ethics approval for this study.

3. Results

Regarding therapy provision plans, a total of 5489 provision plans representing Class I through III (7 for Class I, 1595 for Class II, and 3887 for Class III) were submitted, of which 104 (1.9%) involved the OBGYN field. All 104 provision plans were classified as Class II and accounted for 6.5% of the total Class II RM provision plans. The results of the descriptive analysis are summarized in Fig. 1. With respect to region, provision plans were available in 24 prefectures, which were approximately half of the 47 prefectures, and specifically in Tokyo (33.7%), Osaka (10.6%), and Aichi (8.7%) (Fig. 1a, Sup. Table 1). By population, 74 (71.2%) of the therapeutic provision plans were associated with prefectures with a population of 3 million or more (Fig. 1b). Based on implementing medical institutions, 94 (90.4%) of the provision plans were administered in clinics (Fig. 1c). By modality, PRP accounted for the majority (87 plans, 83.7%), whereas MSC accounted for the balance (17 plans, 16.3%), of which 13 (12.5%) and 4 (3.8%) provision plans involved adipose tissue-derived stem cells (ADSCs) and menstrual blood-derived stem cells (MenSCs), respectively (Fig. 1d). No other MSC sources were available, such as bone marrow-, umbilical cord-, or dental pulp-derived tissues. With respect to targeted diseases, 92 (88.5%) provision plans were for infertility, and the remaining 12 (11.5%) were for menopausal symptoms (Fig. 1e). In terms of targeted tissues, 65 (62.5%) of the provision plans involved the endometrium, 37 (35.6%) were associated with the ovary, and the remaining 2 (1.9%) included both the endometrium and ovary (Fig. 1f). With respect to the route of administration, 93 (89.4%) of the provision plans involved local administration (to endometrium or ovary) and 11 (10.6%) were systemic (intravenous) (Fig. 1g). The number of therapeutic provision plans submitted by year was also evaluated. Until 2018, there were only four provision plans for menopausal symptoms using autologous ADSC; however, since 2019, provision plans involving PRP for infertility increased, with 27 provision plans in 2019 (Fig. 1h). However, the number of new provision plans provided trended downward, particularly in plans involving PRP. On the other hand, the number of provision plans using MSC, particularly in ADSC, gradually increased over the last two years. With respect to disease, while infertility treatment dominated the list of targeted diseases since 2019, the number of provision plans targeting infertility treatment declined along with the decrease in provision plans using PRP, whereas the number of provision plans for menopausal symptoms using MSC increased in 2023 (Fig. 1i).

Statistical analyses of the descriptive characteristics by modality were performed (Table 1). All 87 provision plans with PRP were for infertility treatment, whereas only 5 (29.4%) involving MSC were for it ($P < 0.001$). The provision plans with PRP primarily targeted the endometrium (63 plans, 72.4%), whereas those involving MSC targeted the ovary (13 plans, 76.4%) ($P < 0.001$). In terms of administration route, all provision plans with PRP were administered locally (to endometrium or ovary), whereas almost two-thirds of the provision plans involving MSC were systemic (intravenous) (11 plans, 64.7%) ($P < 0.001$). Furthermore, the provision plans with PRP were mainly carried out in clinics (77 plans, 88.5%) and all provision plans with MSC were done in clinics, none in the hospitals ($P = 0.17$). Regarding regional characteristics, 57 (65.5%) provision plans with PRP and all provision plans with MSC were offered in prefectures with >3 million people ($P = 0.004$).

Next, we investigated the price of RM for the therapeutic provision plans (Table 2). The mean prices of RM using PRP and MSC were 240.8 ± 106.5 and 1832.1 ± 1139.8 thousand yen (mean ± SD), respectively, with provision plans using MSC pricing significantly more ($p < 0.0001$). Focusing on each descriptive characteristic in which statistical analysis could be performed, the mean price of provision plans using PRP administered to the ovary was significantly more expensive compared with that of provision plans using PRP administered to the endometrium (368.3 ± 116.3 vs. 192.2 ± 45.0 thousand yen, $p < 0.001$). The price of the provision plans for PRP at the clinics was significantly more expensive compared with that at hospitals (248.9 ± 110.0 vs. 178.7 ± 38.0 thousand yen, $p = 0.049$). No difference was observed in terms of the population of the prefectures ($p = 0.51$). Among the provision plans using MSCs, there was no clear trend in price with respect to targeted diseases, targeted tissues, and administration route.

Finally, we summarized the status of the research provision plans (Table 3). A total of 184 plans representing Class I through III (27 for Class I, 79 for Class II, and 78 for Class III) were submitted, of which 4 (2.2%) were associated with OBGYN. Of these, one provision plan was classified as Class II and the other three were classified as Class III, which accounted for 1.3% and 3.8% of the total Class II and Class III RM provision plans, respectively. All four plans were administered at university hospitals. The provision plans classified as Class II risk involved the local administration of autologous ADSC for refractory implantation failure. For the provision plans classified as Class III risk, one was for implantation failure using intrauterine administration of autologous peripheral blood lymphocytes, whereas the other two were for advanced or recurrent cervical cancer using systemic administration of tumor-infiltrating lymphocytes, and chemotherapy-resistant or recurrent ovarian cancer using subcutaneous injection of autologous dendritic cells and inactivated tumor cells, respectively. All clinical studies were open-label and single-arm.

4. Discussion

The present study revealed the current status of RM in a specific clinical field from publicly available information collected under the RM Act. We found that the provision plans for both therapy and clinical research in the field of OBGYN consisted of a small portion of RM in Japan. Most therapeutic provision plans, which are all classified as Class II, were administered in clinics in urban areas to treat endometrial infertility by intrauterine administration of PRP.

For the descriptive data, our survey revealed that autologous PRP and ADSC are the major modalities in RM in the field of OBGYN as well as other fields [5,15]. The use of autologous cells is advantageous in terms of immune rejection and infection and readily

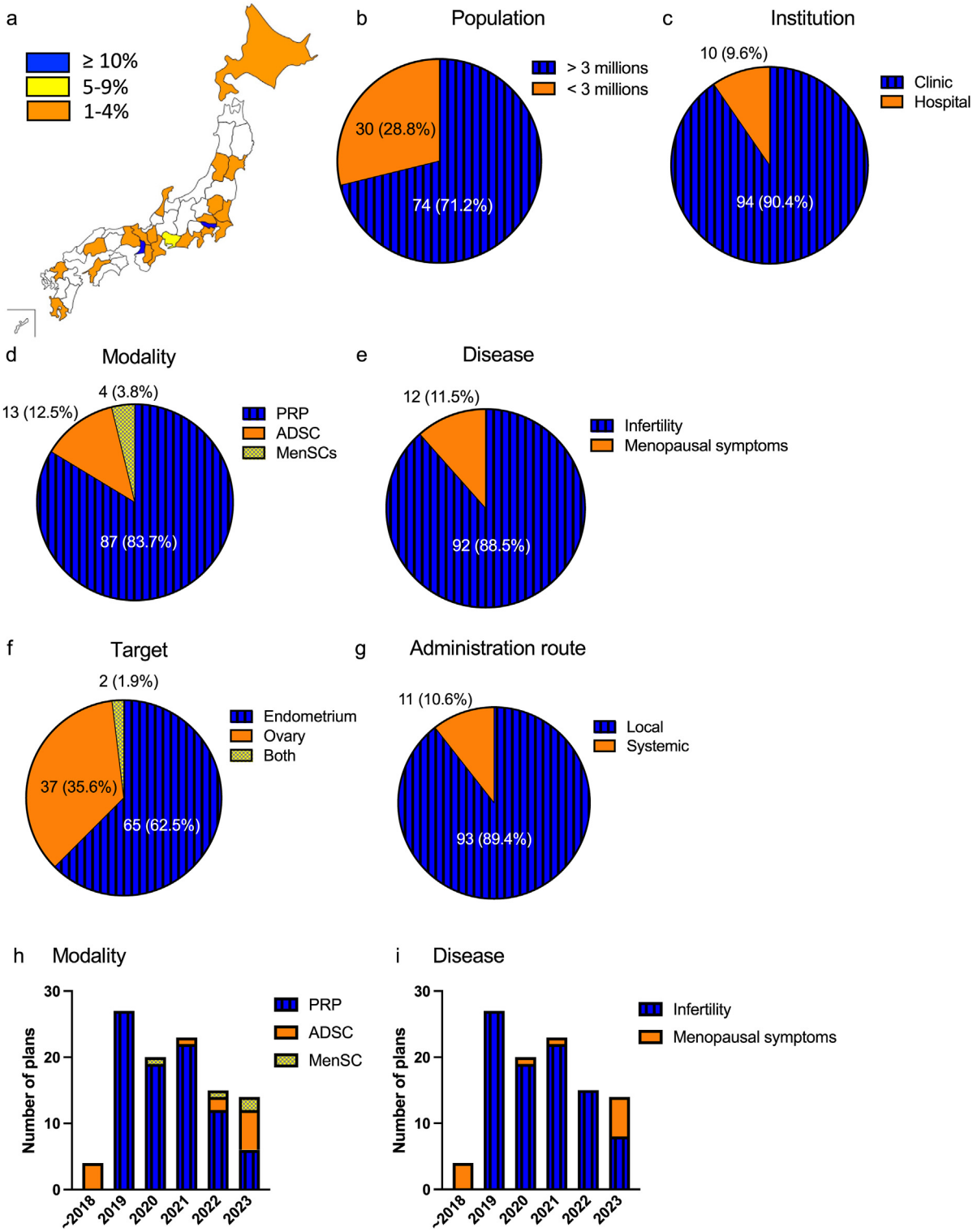

Fig. 1. Descriptive characteristics of regenerative medicine in the field of obstetrics and gynecology in Japan. Characteristics were evaluated by (a) Region, (b) Population, (c) Institution, (d) Modality, (e) Disease, (f) Target region, and (g) Administration route, (h) Annual trend of the number of therapeutic provision plans by each modality, (i) Annual trend of the number of therapeutic provision plans by disease.

adapted to clinical practice; however, there are some issues, such as difficulty standardizing quality and estimating efficacy. Moreover, as mentioned below, the price is also more expensive. The present study also showed that the accessibility of RM in the field of OBGYN under the RM Act differs by locality. A previous report indicated that developing and initiating clinical researches of RM products derived from pluripotent stem cells are only available in developed countries because of financial barriers, a requirement for qualified personnel of RM, and the availability of cell lines [16]. Based on our domestic view, the provision plans for therapy and clinical research

Table 1
Modality of the therapeutic provision plans in the field of obstetrics and gynecology.

Variables, n (%)	PRP, n = 87	MSC, n = 17[a]	P value
Disease			
Infertility	87 (100)	5 (29.4)	<0.001
Menopausal symptoms	0 (0)	12 (70.6)	
Target region			
Endometrium	63 (72.4)	2 (11.8)	<0.001
Ovary	24 (27.6)	13 (76.4)	
Both	0 (0)	2 (11.8)	
Administration route			
Local	87 (100)	6 (35.3)	<0.001
Systemic	0 (0)	11 (64.7)	
Institution			
Hospital	10 (11.5)	0 (0)	0.14
Clinic	77 (88.5)	17 (100)	
Regional population			
<3 million	30 (34.5)	0 (0)	<0.01
>3 million	57 (65.5)	17 (100)	

Abbreviations: PRP, platelet-rich plasma; MSC, mesenchymal stem cell.
[a] MSC includes adipose tissue-derived stem cell and menstrual blood-derived stem cell.

under the RM Act are mainly performed in urban areas, suggesting the involvement of similar issues with qualified personnel and accessibility to cell processing facilities. Therefore, further development of CGT products with pharmaceutical approval under the PMD Act, which can be banked as cell stock and are easily managed by lot as products, is warranted, because the products are distributable and confirmed to be of uniform quality.

To our knowledge, discussions about the price of the RM are rare [16]. Our results indicated that the price of therapeutic provision plans using MSC is approximately eight times more expensive that of PRP. Generally, because CP products using MSC require cell processing, the price of RM using MSC, particularly in autologous cells, becomes more expensive compared with that of PRP. Moreover, the price of RM using PRP administered to the ovary is significantly more expensive compared with that administered to the endometrium, probably because it requires a higher degree of manual labor and injections to both sides. Further discussion on how to optimize the price of RM may be required to increase availability and greater public acceptance.

Table 2
Price of the therapeutic provision plans for each modality in the field of obstetrics and gynecology.

Variables, yen (× 1000, mean ± SD) n for PRP and MSC	PRP, n = 87	P value	MSC, n = 14[a]	P value
Overall	240.8 ± 106.5		1832.1 ± 1139.8	
Disease				
Infertility, n = 87 and 5	240.8 ± 106.5	–	1560.0 ± 859.1	0.52
Menopausal symptoms, n = 0 and 9	–		1983.3 ± 1292.3	
Target region				
Endometrium, n = 63 and 2	192.2 ± 45.0	<0.001	1950.0 ± 1484.9	0.84
Ovary, n = 24 and 10	368.3 ± 116.3		1875.0 ± 1265.6	
Both, n = 0 and 2	–		1500.0	
Administration route				
Local, n = 87 and 6	240.8 ± 106.5	–	1383.3 ± 823.2	0.21
Systemic, n = 0 and 8	–		2168.8 ± 1275.3	
Institution				
Hospital, n = 10 and 0	178.7 ± 38.0	0.049	–	–
Clinic, n = 77 and 14	248.9 ± 110.0		1832.1 ± 1139.8	
Regional population				
<3 million, n = 30 and 0	230.5 ± 86.9	0.51	–	–
>3 million, n = 57 and 14	246.3 ± 115.9		1832.1 ± 1139.8	

Abbreviations: PRP, platelet-rich plasma; MSC, mesenchymal stem cell.
[a] MSC includes adipose tissue-derived stem cell and menstrual blood-derived stem cell and three plans were missing for price information.

Table 3
Research provision plans under the RM Act in the field of obstetrics and gynecology.

No.	Trial ID	Hospital	Year of start	Targeted disease	Risk classification	Modality	Design	Trial phase	Administration route	Progression	Primary outcome
1	jRCTc031200283	Keio university school of medicine	2021	Advanced cervical cancer	3	Lymphocyte (TIL)	Open labeled and single arm	2	Systemic (intravenous)	Suspended	Best overall response rate Adverse events (type, frequency and severity)
2	jRCTc050190121	Kyoto university hospital	2020	Refractory implantation failure	3	Lymphocyte (Peripheral blood)	Open labeled and single arm	0	Local (endometrium)	On going	Implantation rate Pregnancy outcome
3	jRCTb070200001	Fukuoka university hospital	2020	Implantation failure	2	MSC(ADSC)	Open labeled and single arm	2	Local (endometrium)	Closed	Measurement of endometrium thickness Conformation of pregnancy
4	jRCTc051190054	Osaka university hospital	2019	Chemoresistant or recurrence ovarian cancer	3	Dendritic and tumor fusion cells	Open labeled and single arm	1	Local (subcutaneous)	Closed	Adverse events during the clinical trial

Abbreviations: RM Act, the Act on the Safety of Regenerative Medicine; TIL, tumor infiltrating lymphocyte; ADSC, adipose tissue-derived stem cell.

For an overview of the RM, it was previously reported that the RM provision plans in Japan mainly consist of orthopedics, dentistry, and cosmetic use [15]. Our study revealed that only 104 therapeutic provision plans and 4 research provision plans, which are primarily for infertility, have been submitted under the RM Act. This current trend is understandable because clinical reports revealing the safety and partial efficacy of PRP for endometrial infertility were published around 2019–2020 [17,18], even from a Japanese institution [19], which may have been the beginning of RM for infertility in Japan. A therapeutic strategy using autologous MSCs for endometrial and ovarian infertility has also been expected [20,21]. In fact, several phase I clinical trials of intrauterine artery transplantation of autologous bone marrow-derived MSCs and intrauterine transplantation of autologous MenSCs for severe Asherman's syndrome and refractory infertility resulting from injured endometrium demonstrated improvement of thin endometrium, and some cases resulted in successful pregnancy after transplantation without obvious clinical safety concerns [22–24]. With respect to endometrial regeneration, the pathology of Asherman's syndrome was endometrial fibrosis and a decrease in vasculature followed by senescence and deficiency of endometrial MSC [25,26]; therefore, MSC supplementation seems to be a reasonable approach for treating this disease. However, it should be noted that these clinical trials involving PRP and MSC for refractory endometrial infertility or ovarian insufficiency are still in the exploration phase, and no valid evidence for safety and efficacy has yet been established [27–29]. Consequently, clinicians and patients need to understand the limitations of these RMs provided in private practice. For gynecological cancer, only two research provision plans involving RM have been implemented under the RM Act. Some preclinical studies have revealed the anticancer potential of natural killer cells, dendritic cells, gene-edited lymphocytes, such as CAR-T cells, and immune cells derived from allogenic induced pluripotent stem cells for gynecological cancer [14,30–33]. Generally, novel molecular-targeted drugs show remarkable anticancer effects in gynecologic cancers that harbor eligible gene mutations [34]; however, because gynecological cancers without targeted gene mutations are resistant to these drugs, the development of novel therapeutic modalities regarding RM for these types of cancers may be an option. In addition, there is no provision plan for therapy and clinical research for perinatal diseases. Fetal therapy using a cellular sheet to treat fetuses with myelomeningocele [35,36] and ex vivo gene therapy to treat hypophosphatasia [37] are expected to have future clinical applications. In this field, however, the following issues remain to be addressed for further clinical application: the limited number of facilities that can provide fetal therapy, safety concerns to mothers, ethical issues involved in fetal therapy, and the lack of appropriate animal models. Therefore, a discussion of such ethical and practical problems for future clinical applications is warranted.

This study has several limitations. First, the therapeutic provision plans that have been discontinued were not accessible in the e-Regenerative Medicine. Those not listed at the time of study inclusion were consequently omitted from the analysis. Second, numerous therapeutic provision plans for cancer exhibit a comprehensive designation only targeting “Cancer,” [15] potentially leading to an underestimation of the number of therapeutic provision plans specifically targeting gynecological cancers. Third, although the brief summary of regular reports, which are submitted to the certified committees and the Minister of Health, Labour, and Welfare from medical institutions, is annually discussed on the Health Science Council, Regenerative Medicine Evaluation Committee, the details of the regular reports were not available on the websites. Thus, they could not be analyzed individually in our report. In addition, the regular reports include the number of provided RMs and information on their effectiveness and safety, but it has been noted that they are doubtful whether sufficient information for determining therapeutic appropriateness is reported [38]. These points are limitations in the review for RMs under the RM Act.

Nevertheless, this unique Japanese legal framework, which enables us to grasp the status of not only clinical research but also private practice, is useful for discussing the development of RM in Japan. Hopefully, our results provide a better understanding of the strength of the RM Act and shall prompt a worldwide discussion on the appropriate regulation for RM.

Approval by ethics committee

Not applicable.

Informed consent for participation and publication

Not applicable.

Availability of data and material

The data used and/or analyzed during the current study are available from the websites, the e-Regenerative Medicine (https://saiseiiryo.mhlw.go.jp/) for therapeutic provision plans and the Japan Registry of Clinical Trials (jRCT) (https://jrct.niph.go.jp/) for research provision plans.

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Author contributions

Conceptualization: SH, YU, KM; Methodology: SH, RY, YU, KM; Data collection: SH; Statistical analysis: SH; Interpretation of data: SH, SAK, RY, YU, KM, Y Kasahara, Y Kishi; Project administration: SH, RY, AO; Supervision: AO; Writing—original draft: SH; Writing—review and editing: SAK, RY, YU, KM, Y Kasahara, Y Kishi, AO. All the authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2024.08.003.

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