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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Analysis of severe psychological stressors in women during fertility treatment: Japan-Female Employment and Mental health in Assisted reproductive technology (J-FEMA) study

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Abstract

Purpose To identify risk factors for severe psychological stress in women undergoing fertility treatment.

Methods This cross-sectional, multi-center study was conducted from August to December 2018. We recruited 1672 subjects who completed an anonymous, self-reported questionnaire regarding fertility treatment, conditions at work and home, and psychological stress using K6 score, which estimates psychological distress during the previous 30 days. We further focused our analysis on 1335 subjects who were working when starting fertility treatment.

Results Of 1672 women, mean K6 score (range 0–24) was 4.8 ± 4.4, including 103 women (6.2%) with K6 score ≥ 13 (high K6), and classified as probable severe psychological distress. Multivariate logistic regression analysis showed that high K6 was strongly associated with low annual family income of ≤ USD55,700 (JPY6 million) (odds ratio [OR] 1.89, 95% confidence interval [CI] 1.04−3.42), infertility duration of ≥ 2 years (OR 1.87, 95% CI 1.08−3.25), and no experience of childbirth (OR 2.04, 95% CI 1.05−3.97). Focusing on 1335 working women, 266 (19.9%) experienced resignation from work. High K6 was strongly associated with low family income (OR 2.83, 95% CI 1.52−5.28), cessation of professional duties (OR 2.08, 95% CI 1.05–4.14), infertility-related harassment in the workplace (OR 2.07, 95% CI 1.08−3.98), and perceived difficulties to continue working during fertility treatment (OR 2.94, 95% CI 1.15−7.50).

Conclusion Severe psychological stressors in women during fertility treatment included low family income, long infertility duration, childlessness, infertility-related harassment, and perceived difficulty in working conditions or cessation from work. Establishment of mental health care support systems is urgently required in this population.

Keywords Assisted reproductive technology · Employment · Fertility treatment · K6 score · Stress

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Introduction

Infertility is one of the most stressful conditions for couples who desire children [1]. Half of all women undergoing fertility treatment experience some level of anxiety and depressive symptoms [2]. These include psychological stress and anxiety derived from instability regarding the future, unsuccessful pregnancy, high medical costs, and relationships with partners, family, and colleagues. Whether psychological stress directly interferes with human fertility still remains controversial, though an increased risk of infertility due to preconception stress has been reported [3–5].

In 2015, the average age of Japanese women at first marriage and first childbirth were 29.4 and 30.7 years old, respectively [6]. However, female ovarian function declines with age, a rate of decrease which accelerates in women aged 35 or older [7–10], leading to increasing rates of women who require fertility treatment. According to a national assisted reproductive technology (ART) registry database in Japan, ART treatment including in vitro fertilization (IVF) have more than doubled in the last decade, increasing from 161,164 cycles in 2007 to 448,210 cycles in 2017 [11, 12]. Furthermore, the largest number of women by age undergoing ART treatment rose from 35 to 39 years during this period [11, 12].

During this time, the number of working women has also continued to rise, with 44.5% of women employed in 2017, 70% of whom were of reproductive age [13]. ART treatment requires frequent outpatient visits for clinical examinations, and numerous procedures including ovarian stimulation injections, oocyte retrieval, embryo transfer, and pregnancy testing. Therefore, working women may feel particular difficulty during the course of fertility treatment, given the limited time permitted away from professional obligations. Furthermore, despite the reproductive age limits associated with successful conception, many women may perceive a lack of understanding, sensitivity, and flexibility in their company work systems allowed for fertility treatment.

In fact, psychological distress and mental disorders in infertile Japanese women during fertility treatment have been reported [14, 15]. Given these barriers, the aim of this study was to assess the current mental health situation in Japan among women undergoing fertility treatment and identify the risk factors for severe mental stress in this population.

Materials and methods

Study design

The Japan-Female Employment and Mental health in ART (J-FEMA) study was organized by Departments of Public Health and Obstetrics and Gynecology, Juntendo University Faculty of Medicine in November 2017, establishing a database of fertility treatment, as well as work and home lifestyle information. It was a cross-sectional, multi-center study.

Subjects and measurements

Of 1930 infertile women who were given questionnaires, 1727 women responded (a response rate: 89.5%) from August to December 2018 at four ART facilities in Tokyo, Japan (Sugiyama Clinic Shinjuku, Sugiyama Clinic Marunouchi, Saint Mother Obstetrics and Gynecology Clinic, and Takasaki ART Clinic). Of these, we analyzed 1672 subjects excluding 55 subjects, 36 of whom were undergoing mental health treatment and 19 with missing Kessler Six-question Psychological Distress Scale (K6) data. Regarding stress in workplace, we focused on 1335 women who reported working at the time of starting their fertility treatment.

Various questions were employed in the questionnaire including patient age, education background, marital status, living with a partner, life and habits, pregnancy history, fertility treatment, and adjuvant treatment for infertility. Furthermore, work-related questions included annual family income; work environment including employment status, unexpected leave for fertility treatment, infertility-related harassment experience, ability to consult with one`s employer about fertility treatment, and difficulty of balancing fertility treatment and work. To evaluate non-specific psychological distress, we used the K6 score [16] in, which estimates how frequently respondents have experienced symptoms of psychological distress during the previous 30 days. Responses are recorded using a five-category scale (4 = all of the time, 3 = most of the time, 2 = some of the time, 1 = a little of the time, and 0 = none of the time), yielding a score range of 0–24. The K6 scores between 0 and 7, 8 and 12, and 13 and 24 indicate a very low possibility, a moderate probability, and high likelihood of the respondents to develop a psychological disorder, respectively. The K6 score has been translated into Japanese, and has been shown to have acceptable reliability and validity for measuring levels of psychological distress in a Japanese population with a high value of the areas under receiver operating characteristic curves [17].

We defined a K6 cut-off score of ≥ 13 (high K6) as indicative of a high probability of severe psychological distress as per previous reports [18].

Ethics

Written informed consent was obtained from all participants and there was no compensation for participation. This study was approved by the local ethics committee of Juntendo University Faculty of Medicine (No. 18-008, Tokyo, Japan) and Sugiyama Clinic (No. 18-001; Tokyo, Japan).

Statistical analyses

We adjusted all the variables and calculate odds ratio (OR) of high K6 (K6 score ≥ 13). Potential risk factors for high K6 were examined in the multivariable logistic regression model, including ART facility, age, educational background, marital status, living with a partner, annual family income, duration of infertility, past history of childbirth, fertility treatment, adjuvant treatment, cumulative expense for fertility treatment, fitness habits, smoking, and alcohol. In this study, the number of previous clinical pregnancy loss was not associated with K6 score in univariate analysis, thus a history of pregnancy loss was not included in the variables in multivariate analysis (Supplemental Table 1). All probability values for statistical tests were two-tailed, and values of $p < 0.05$ were regarded as statistically significant. All statistical analyses were performed using SAS Studio 3.8 (SAS Institute, Inc., Cary, NC, USA).

Results

Of all participants, 103 women (6.2%) reported a high K6 score, indicating potential for severe psychological distress. The characteristics of subjects are summarized by K6 score in Table 1. Women in the high K6 group had significantly lower family income as well as less experience of pregnancy and childbirth ($p < 0.01, = 0.02$, and 0.02, respectively) compared to those with lower K6 scores. Multivariate logistic regression analysis showed that high K6 is strongly associated with low family income defined as ≤ USD55,700 (JPY6 million) (OR 1.89, 95% CI 1.04−3.42), long duration of infertility of ≥ 2 years (OR 1.87, 95% CI 1.08−3.25), and no experience of childbirth (OR 2.04, 95% CI 1.05−3.97) (Table 2).

Characteristics of selected working women by K6 score are shown in Table 3. Working women in the high K6 group had significantly lower family income ($p < 0.01$). When starting fertility treatment, the proportion of permanent workers, non-permanent workers, and self-employed workers were 77.7% (770 women), 14.8% (147 women), and 7.5% (74 women), respectively. Regarding work situation, 266 women (19.9%) stopped work or changed occupation as a result of their fertility treatment. Among the 86 working women with high K6 score, there was a significantly higher rate of labor turnover (31.4%, 27 women, $p < 0.01$) and infertility-related harassment experience in the workplace (17.5%, 14 women, $p < 0.01$) compared to those without high K6 scores. Most women (82.8%, 1046 women) reported feeling some difficulty balancing fertility treatment and work obligations due to the frequency of needed outpatient visits (64.7%, 677 women), lack of time for hospital visits (59.0%, 617 women), mental burden (46.8%, 490 women), high medical cost (33.6%, 351 women), and lack of understanding from colleagues in the workplace (18.7%, 196 women).

Multivariate logistic regression analysis of working women showed that high K6 was strongly associated with inadequate family income (OR 2.83, 95% CI 1.52–5.28), experience of resignation from work (OR 2.08, 95% CI 1.05–4.14), infertility-related harassment in the workplace (OR 2.07, 95% CI 1.08–3.98), and perceived difficulties in continuing work during fertility treatment (OR 2.94, 95% CI 1.15–7.50) (Table 4).

Discussion

This study revealed that 6.2% of women undergoing fertility treatment reported markedly high K6 scores with high likelihood of development of severe mental health disorders [18]. The incidence of anxiety and depressive symptoms in infertile couples is known to be higher than that in fertile controls or the general population [19]. A large Danish study of 42,000 women who underwent ART treatment demonstrated that 35% were diagnosed as depression prior to treatment [20]. Chen, et al. reported that 40% of women with first visit to an ART clinic had psychiatric disorders, including generalized anxiety disorder (23.2%), major depressive disorder (17.0%), and dysthymic disorder (9.8%) [2]. Moreover, Shani et al. reported that 9.4% of infertile women had suicidality [21]. Although most women can adjust to emotional stress after reproductive failure in IVF treatment [22], severe psychological distress may lead to suicidal ideation, suggesting that a substantial portion of women with high K6 scores in our study are likely to be at high risk for severe psychological illness including suicidality. According to K6 score data in employees in Japan reported by Fushimi, et al., Japanese working women aged 49 years or less with high K6 was 13.3% (107/802 women) [23]. In our study, there is no K6 score data in fertile women as a control, yet the proportion of the patients with high K6 was not larger, compared with those in previous reports [2, 20, 21, 23].

According to another study, women with a K6 score of ≥ 8 had significantly more experience of unsuccessful

Table 1 Patient characteristics by K6 score

	K6 score ≥ 13 $n = 103$	K6 score < 13 $n = 1569$	p value
Age, years	37.2 ± 5.3	37.6 ± 4.8	0.33
Educational background			
High school or junior high school	14 (13.7%)	203 (13.0%)	0.57
Junior college or professional school	42 (41.2%)	548 (35.1%)	
University	42 (41.2%)	717 (45.9%)	
Graduate school	4 (3.9%)	93 (6.0%)	
Marital status			
Married	98 (96.1%)	1521 (97.1%)	0.50
Unmarried	4 (3.9%)	46 (2.9%)	
Living with a partner	98 (96.1%)	1511 (96.8%)	0.57
Annual family income, USD[b]	71,530 ± 32,190	81,980 ± 31,920	< 0.01[a]
Employment			
Employed	92 (89.3%)	1330 (84.8%)	0.25
Unemployed	10 (9.7%)	236 (15.0%)	
Duration of infertility, year	3.5 ± 2.8	3.0 ± 2.6	0.06
Pregnancy history			
Gravida	40 (40.4%)	802 (52.6%)	0.02[a]
Parity	11 (11.1%)	327 (21.4%)	0.02[a]
Fertility treatment			
Non-ART treatment	33 (32.0%)	421 (26.8%)	0.25
ART treatment	69 (67.6%)	1130 (72.9%)	
Adjuvant treatment in fertility treatment			
Acupuncture	23 (22.3%)	310 (19.8%)	0.52
Herbal medicine	26 (25.2%)	308 (19.6%)	0.16
Body massage/chiropractic treatment	9 (8.7%)	87 (5.5%)	0.18
Yoga	10 (9.7%)	133 (8.5%)	0.59
Nutrition supplementation	56 (54.4%)	691 (44.0%)	0.05
Total	62 (60.2%)	820 (52.3%)	0.13
Cumulative expense for fertility treatment[b]			
< USD9,300 (JPY1 million)	50 (52.1%)	727 (48.4%)	0.20
USD9,300–27,800 (JPY1-3 million)	27 (28.1%)	545 (36.3%)	
> USD27,800 (JPY3 million)	19 (19.8%)	231 (15.4%)	
Lifestyle factors[c]			
Fitness habit	13 (12.6%)	271 (17.3%)	0.28
Smoking	3 (2.9%)	46 (2.9%)	0.25
Alcohol	42 (42.0%)	671 (43.8%)	0.76

Results are expressed as mean ± SD or *n* (%). *SD*, standard deviation; *n*, number of women; *USD*, United States dollar; *JPY*, Japanese yen; *ART*, assisted reproductive technology

[a]Statistically significant values, $p < 0.05$

[b]Converted to USD from JPY using average USD exchange rate in May 2020 published by Bank for International Settlements (JPY107.8/USD)

[c]Fitness habit is more than 30 min daily exercise at least 2 days a week for 1 year or more. Smoking includes current smoker only. Alcohol is one time or more per week of drink

conception after multiple treatment attempts, spontaneous or induced abortion and stillbirth, had more unexplained infertility, less history of childbirth, and lower family income, compared with those in normal K6 ranges [14]. In our study, severe psychological distress associated with a K6 score of ≥ 13 included long infertility period, absence of history of childbirth, and low family income. Although the risk factors of psychological stress were similar to previous reports, when focusing on severe mental stress corresponding to psychiatric disorders in our study, prolonged duration of infertility, childlessness, and severe constraints on family budgets suggest themselves to be

Table 2 Risk factors of severe psychological stress in all patients on multivariate regression analysis

Independent variable, $n = 1672$	Odds ratio (95% CI)[a]
ART facility	
A	Reference
B	0.82 (0.46–1.47)
C	0.79 (0.40–1.54)
D	1.06 (0.59–1.88)
Age	
< 29 years	Reference
30–39 years	0.75 (0.30–1.86)
≥ 40 years	0.66 (0.25–1.76)
Educational background	
High school or junior high school	Reference
Junior college or professional school	1.18 (0.62–2.25)
University	1.23 (0.62–2.44)
Graduate school	1.10 (0.33–3.65)
Marital status	
Married	Reference
Unmarried	1.72 (0.54–5.49)
Living with a partner	
Yes	Reference
No	1.18 (0.37–3.79)
Annual family income[b]	
> USD74,200 (JPY8 million)	Reference
USD55,700–74,200 (JPY6-8 million)	1.27 (0.72–2.27)
< USD55,700 (JPY6 million)	1.89 (1.04–3.42)[c]
Duration of infertility	
< 2 years	Reference
≥ 2 years	1.87 (1.08–3.25)[c]
Past history of childbirth	
Yes	Reference
No	2.04 (1.05–3.97)[c]
Fertility treatment	
Non-ART treatment	Reference
ART treatment	0.75 (0.43–1.34)
Adjuvant treatment in fertility treatment[d]	
No	Reference
Yes	1.42 (0.91–2.20)
Cumulative expense for fertility treatment[b]	
< USD9,300 (JPY1 million)	Reference
USD9,300–27,800 (JPY1-3 million)	0.73 (0.41–1.31)
> USD27,800 (JPY3 million)	1.18 (0.59–2.36)
Fitness habit[e]	
Yes	Reference
No	1.72 (0.92–3.23)
Smoking	
Never smoker	Reference
Former smoker	1.45 (0.92–2.28)
Current smoker	0.83 (0.24–2.90)
Alcohol[f]	
No	Reference
Yes	0.96 (0.62–1.48)

CI, confidence interval; *ART*, assisted reproductive technology; *USD*, United States dollar; *JPY*, Japanese yen; *n*, number of women

[a]The logistic regression model included ART facility, age, educational background, marriage state, living with a partner, family income, duration of infertility, past history of childbirth, fertility treatment, adjuvant treatment, cumulative expense for fertility treatment, fitness habits, smoking, alcohol

[b]Converted to USD from JPY using average USD exchange rate in May 2020 published by Bank for International Settlements (JPY107.8/USD)

[c]Statistically significant values

[d]Adjuvant treatment in infertility includes acupuncture, body massage, finger-pressure therapy, herbal medicine, yoga, chiropractic treatment, and nutrition supplementation

[e]Fitness habit is more than 30 min daily exercise at least 2 days a week for 1 year or more. [f]Alcohol is one time or more per week of drink

some of the fundamental mental stressors associated with fertility treatment.

Regarding family incomes in 2017, according to The Ministry of Health Labor and Welfare in Japan, the average incomes for a couple in their thirties and forties were USD52,900 (JPY5.7 million) and USD64,900 (JPY7.0 million), respectively, [24], indicating that a large number of infertile patients with incomes of ≤ USD55,700 (JPY6 million) may be particularly impacted by expensive medical costs associated with treatment and not covered by health insurance. In our study, 51.4% of participants reported a cumulative medical expense for fertility treatment of ≥ USD9,300 (JPY1.0 million); 15.6% reported a cost of ≥ USD27,800 (JPY3.0 million). In Japan, a financial subsidy for fertility treatment, primarily ART treatment, is offered to couples in which the female partner is ≤ 42 years-old and making a combined income of ≤ USD67,700 (JPY7.3 million) [25]. However, our study found that if couples with low family income receive financial support, they may still feel anxiety and psychological stress from financial problems created by fertility treatment, childbirth, and child-rearing in their future.

Exposure to work-related stress can affect mental health. When analyzing data in the subgroup of working women in our study population, severe mental stressors included inadequate family income, resignation from work, infertility-related harassment in the workplace, and feelings of difficulty regarding continuing work during fertility treatment. Stressful work environments, such as those which are permissive to infertility-related harassment, as well as those which force women to leave their jobs, remain a serious problem for Japan, which has struggled unsuccessfully with

Table 3 Characteristics of patients employed at start of fertility treatment by K6 score

	K6 score ≥ 13 (high K6) $n = 86$	K6 score < 13 $n = 1249$	p value
Age, years	37.0 ± 5.4	37.5 ± 4.7	0.41
Annual family income, USD[a]	71,200 ± 33,640	86,040 ± 32,330	< 0.01[b]
Duration of infertility, years	3.5 ± 2.9	3.1 ± 2.6	0.11
Pregnancy history			
Gravida	34 (40.5%)	628 (51.3%)	0.06
Parity	11 (13.1%)	249 (20.3%)	0.12
Fertility treatment			
Non-ART treatment	28 (32.6%)	328 (26.3%)	0.21
ART treatment	57 (67.1%)	909 (73.5%)	
Employment type			
Permanent worker	41 (75.9%)	729 (77.8%)	0.82
Non-permanent worker	8 (14.8%)	139 (14.8%)	
Self-employed worker	5 (9.3%)	69 (7.4%)	
Employment status			
Continued employment	57 (66.3%)	987(80.6%)	< 0.01[b]
Changed occupation	2 (2.3%)	62 (5.1%)	
Cessation	27 (31.4%)	175 (14.3%)	
Unexpected leave for fertility treatment	49 (58.3%)	693 (56.8%)	0.82
Infertility-related harassment experience in workplace	14 (17.5%)	89 (7.5%)	< 0.01[b]
Able to consult to employer about fertility treatment	50 (61.0%)	700 (59.9%)	0.74
Difficulty balancing fertility treatment and work	77 (92.8%)	984 (82.1%)	0.02[b]

Results are expressed as mean ± SD or *n* (%). *SD*, standard deviation; *n*, number of women; *USD*, United States dollar; *ART*, assisted reproductive technology

[a]Converted to USD from Japanese yen JPY using average USD exchange rate in May 2020 published by Bank for International Settlements (JPY107.8/USD)

[b]Statistically significant values, $p < 0.05$

declining birth rates. In 2017, The Ministry of Health Labor and Welfare in Japan conducted a questionnaire survey on the balance between fertility treatment and work in Japanese companies [26]. Of 779 companies answering, 39% had female employees undergoing fertility treatment, but 70% had no support system for these employees. Of the remaining 30% with support systems, organization-based systems were available in only a few companies, with 6.2% providing leave and 1.9% providing expense subsidies. Even in those who underwent fertility treatment, only 42.9% had support systems for fertility treatment by their companies. Furthermore, greater than 80% of the women in our study felt that it was impossible to continue both work and fertility treatment. In other words, a large number of infertile women appear not to visit a fertility clinic if working in unfavorable work environments. As such, establishment of a work environment that supports working women during fertility treatment is urgently needed. Remote work, which became common in COVID-19 pandemic, and a life support for household work from their husbands are one of the solutions for achieving a balance between work and fertility treatment.

To reduce psychological stress in infertile women, it may be particularly important to focus on shortening the time to pregnancy and childbirth as much as possible. However, compared to other mammalian species, the monthly fecundity rate in humans is extraordinarily low at 20% [27]. Therefore, even with IVF treatment, the cycle-based clinical pregnancy rate is fundamentally low at 15–40% [28, 29]. Moreover, the incidence of spontaneous pregnancy loss rises at an accelerating rate with maternal age over 35 years old [30]. As such, aging in infertile women has been linked to delaying time to conception. In Japan, IVF treatment using donor eggs or embryos is almost not allowed due to sociocultural factors. Policies on adoption are also strict. Treatment options to conceive are limited in advanced aged women with a history of reproductive failures after IVF treatment. Therefore, the establishment of Japanese healthcare systems and legal framework for women undergoing fertility treatment, as well as improvement of hospital environment to provide sufficiently highly pregnancy outcomes, may be warranted.

The adverse effect of mental stress on pregnancy still remains controversial, but anxiety disorders and depressive symptoms have a potential risk for the increased rates of both infertility and pregnancy loss and psychological support may help improve pregnancy outcomes [3–5, 31, 32].

Table 4 Risk factors of severe psychological stress in patients employed at start of fertility treatment on multivariable analysis

Independent Variable, $n = 1335$	Odds ratio (95% CI)[a]
Age	
< 29 years	Reference
30–39 years	0.63 (0.25–1.60)
≥ 40 years	0.69 (0.25–1.86)
Annual family income[b]	
> USD74,200 (JPY8 million)	Reference
USD55,700–74,200 (JPY6-8 million)	1.36 (0.74–2.52)
< USD55,700 (JPY6 million)	2.83 (1.52–5.28)[c]
Duration of infertility	
< 2 years	Reference
≥ 2 years	1.55 (0.87–2.78)
Past history of childbirth	
Yes	Reference
No	1.39 (0.71–2.75)
Fertility treatment	
Non-ART treatment	Reference
ART treatment	0.64 (0.37–1.09)
Employment type	
Permanent worker	Reference
Non-permanent worker	0.81 (0.35–1.86)
Self-employed worker	1.12 (0.40–3.17)
Employment status	
Continued employment	Reference
Changed occupation	0.46 (0.11–1.99)
Employment separation	2.08 (1.05–4.14)[c]
Unexpected leave for fertility treatment	
No	Reference
Yes	1.11 (0.68–1.79)
Infertility-related harassment experience in workplace	
No	Reference
Yes	2.07 (1.08–3.98)[c]
Able to consult to employer about fertility treatment	
Yes	Reference
No	1.20 (0.73–1.98)
Difficulty balancing fertility treatment and work	
No	Reference
Yes	2.94 (1.15–7.50)[c]

USD, United States dollar; *ART*, assisted reproductive technology; *n*, number of women

[a]The logistic regression model included age, family income, duration of infertility, past history of childbirth, fertility treatment, employment status, sudden day off, infertility-related harassment, possible to consult to an employer about fertility treatment, difficulty of balancing fertility treatment and work

[b]Converted to USD from JPY using average USD exchange rate in May 2020 published by Bank for International Settlements (JPY107.8/USD)

[c]Statistically significant values

Therefore, psychological stressors from both fertility treatment as well as the workplace may decrease pregnancy outcomes, leading to a vicious cycle of stress and reproductive failure [33]. Conversely, beneficial effects of mental care on infertility and pregnancy loss have been reported [1, 4, 34, 35]. The development and introduction of support systems may improve mental health, leading to shortening time to pregnancy in infertile women.

Regarding limitations, pregnancy outcomes and time-dependent changes are not reflected in our cross-sectional, questionnaire-based study. Further research is warranted to explore these aspects of infertility care.

In conclusion, this study identified several severe psychological stressors among women undergoing fertility treatment including low family income, long duration of infertility, and no history of childbirth. To reduce the psychological burden in infertile women, establishment of mental health care systems and support for continued work during fertility treatments, is urgently required.

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Author contributions YI: protocol/project development, data analysis, manuscript writing/editing, discussion. KK: protocol/project development, data collection, manuscript writing/editing, discussion. ME: protocol/project development, data analysis, discussion. AT: data collection. RS: data collection. KN: data collection. YS: data collection. YK: data collection. KT: data analysis, discussion. YI: discussion. GAD: manuscript editing. TT: discussion, supervision. AI: supervision. ST: supervision.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was approved by the local ethics committee of Juntendo University, Faculty of Medicine (No. 17-316) and Sugiyama Clinic Shinjuku (No. 18-001) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Rooney KL, Domar AD (2018) The relationship between stress and infertility. Dialogues Clin Neurosci 20:41–47
2. Chen TH, Chang SP, Tsai CF, Juang KD (2004) Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 19:2313–2318
3. Lynch CD, Sundaram R, Maisog JM, Sweeney AM, Buck Louis GM (2014) Preconception stress increases the risk of infertility: results from a couple-based prospective cohort study–the LIFE study. Hum Reprod 29:1067–1075
4. Domar AD, Clapp D, Slawsby EA, Dusek J, Kessel B, Freizinger M (2000) Impact of group psychological interventions on pregnancy rates in infertile women. Fertil Steril 73:805–811
5. Gourounti K, Anagnostopoulos F, Vaslamatzis G (2011) The relation of psychological stress to pregnancy outcome among women undergoing in-vitro fertilization and intracytoplasmic sperm injection. Women Health 51:321–339
6. The Ministry of Health Labor and Welfare in Japan. Overview of vital statistics in 2015. https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai15/dl/kekka.pdf. 2016.
7. Broekmans FJ, Soules MR, Fauser BC (2009) Ovarian Aging: Mechanisms and Clinical Consequences. Endocr Revi 30:465–493
8. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF (1992) Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 7:1342–1346
9. Schwartz D, Mayaux MJ (1982) Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. Federation CECOS N Engl J Med 306:404–406
10. te Velde ER, Pearson PL (2002) The variability of female reproductive ageing. Hum Reprod Update 8:141–154
11. Irahara M, Kuwahara A, Iwasa T, Ishikawa T, Ishihara O, Kugu K et al (2017) Assisted reproductive technology in Japan: a summary report of 1992–2014 by the Ethics Committee, Japan Society of Obstetrics and Gynecology. Reprod Med Biol 16:126–132
12. Ishihara O, Jwa SC, Kuwahara A, Katagiri Y, Kuwabara Y, Hamatani T et al (2020) Assisted reproductive technology in Japan: a summary report for 2017 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol 19:3–12
13. The Ministry of Internal Affairs and Communications in Japan. Labor force survey from statistics bureau. https://www.stat.go.jp/data/roudou/2.html. 2018.
14. Takaki J, Hibino Y (2014) Family-related opinions and stressful situations associated with psychological distress in women undergoing infertility treatment. Int J Environ Res Public Health 11:9068–9081
15. Matsubayashi H, Hosaka T, Izumi S, Suzuki T, Makino T (2001) Emotional distress of infertile women in Japan. Hum Reprod 16:966–969
16. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL et al (2002) Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med 32:959–976
17. Furukawa TA, Kawakami N, Saitoh M, Ono Y, Nakane Y, Nakamura Y et al (2008) The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. Int J Methods Psychiatr Res 17:152–158
18. Prochaska JJ, Sung HY, Max W, Shi Y, Ong M (2012) Validity study of the K6 scale as a measure of moderate mental distress based on mental health treatment need and utilization. Int J Methods Psychiatr Res 21:88–97
19. De Berardis D, Mazza M, Marini S, Del Nibletto L, Serroni N, Pino MC et al (2014) Psychopathology, emotional aspects and psychological counselling in infertility: a review. Clin Ter 165:163–169
20. Sejbaek CS, Hageman I, Pinborg A, Hougaard CO, Schmidt L (2013) Incidence of depression and influence of depression on the number of treatment cycles and births in a national cohort of 42,880 women treated with ART. Hum Reprod 28:1100–1109
21. Shani C, Yelena S, Reut BK, Adrian S, Sami H (2016) Suicidal risk among infertile women undergoing in-vitro fertilization: Incidence and risk factors. Psychiatry Res 240:53–59
22. Verhaak CM, Smeenk JM, Evers AW, Kremer JA, Kraaimaat FW, Braat DD (2007) Women's emotional adjustment to IVF: a systematic review of 25 years of research. Hum Reprod Update 13:27–36
23. Fushimi M, Saito S, Shimizu T, Kudo Y, Seki M, Murata K (2012) Prevalence of psychological distress, as measured by the Kessler 6 (K6), and related factors in Japanese employees. Commun Ment Health J 48:328–335

24. The Ministry of Health Labor and Welfare in Japan. Comprehensive survey of living conditions. https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa18/index.html. 2017.
25. The Ministry of Health Labor and Welfare in Japan. Support for couples suffering from infertility. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000047270.html. 2016.
26. The Ministry of Health Labor and Welfare in Japan. Investigation about problems to affect in balance of infertility treatment and work. https://www.mhlw.go.jp/stf/houdou/0000197936.html. 2017.
27. Evers JLH (2002) Female subfertility. Lancet 360:151–159
28. Leijdekkers JA, Eijkemans MJC, van Tilborg TC, Oudshoorn SC, McLernon DJ, Bhattacharya S et al (2018) Predicting the cumulative chance of live birth over multiple complete cycles of in vitro fertilization: an external validation study. Hum Reprod 33:1684–1695
29. Verhagen TE, Dumoulin JC, Evers JL, Land JA (2008) What is the most accurate estimate of pregnancy rates in IVF dropouts? Hum Reprod 23:1793–1799
30. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M (2000) Maternal age and fetal loss: population based register linkage study. BMJ 320:1708–1712
31. Li W, Newell-Price J, Jones GL, Ledger WL, Li TC (2012) Relationship between psychological stress and recurrent miscarriage. Reprod Biomed Online 25:180–189
32. Sugiura-Ogasawara M, Furukawa TA, Nakano Y, Hori S, Aoki K, Kitamura T (2002) Depression as a potential causal factor in subsequent miscarriage in recurrent spontaneous aborters. Hum Reprod 17:2580–2584
33. Kuroda K (2018) Lifestyle habits and pregnancy loss. In: Kuroda K, Brosens JJ, Quenby S, Takeda S (eds) Treatment strategy for unexplained infertility and recurrent miscarriage. Springer Singapore, Singapore, pp 95–104
34. Clifford K, Rai R, Regan L (1997) Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod 12:387–389
35. Stray-Pedersen B, Stray-Pedersen S (1984) Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol 148:140–146