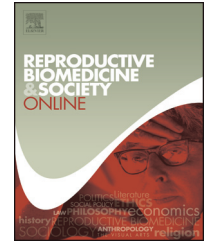




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ARTICLE

Lack of association between receiving ART treatment and parental psychological distress during pregnancy: Preliminary findings of the Japan Environment and Children's Study

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Abstract In a nationwide population-based birth cohort study in Japan, pregnant women and their partners were evaluated for psychological distress as part of the first and second/third trimester health checks. Participants were divided into three groups: an infertility group receiving assisted reproductive technology (ART) treatment (239 mothers and 151 fathers); an infertility group receiving non-ART treatment (350 mothers and 215 fathers); and a spontaneous pregnancy group (8514 mothers and 5110 fathers). Data on maternal and child health as well as basic characteristics were collected via medical records and self-administered questionnaires. The Kessler Six-item Psychological Distress Scale was employed for eligible women and their partners. Multivariate logistic regression analysis was used to evaluate the association between psychological distress experienced during pregnancy and ART treatment, with adjustment for potential confounders such as basic health status and socio-economic status. The mothers who received ART treatment suffered less psychological distress than the mothers in the other two groups. In multivariate analysis adjusted for background characteristics, no significant association was observed between persistent maternal distress and ART

¹ Members of the JECS Group are listed in Appendix.

treatment (adjusted odds ratio 0.79, 95% confidence interval 0.49–1.26). Higher socio-economic status among couples receiving ART treatment may explain, in part, the lack of association between ART treatment and parental distress during pregnancy. 

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Introduction

Techniques of assisted reproductive technology (ART) such as in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are well-established, widely accepted treatments that are being used increasingly often in Japan as a consequence of the growing popularity of delayed marriage. The number of babies born following ART treatment is increasing each year, and reached 42,554 in 2013 (Japan Society of Obstetrics and Gynecology, 2013), equivalent to 4.2% of total births or one per 24 live births. The adverse influence of ART treatment on perinatal outcomes has been investigated (Hansen et al., 2002; Niemitz and Feinberg, 2004). However, the precise causes of these pregnancy complications are not yet fully understood, and previous systematic reviews suggest that there still seems to be great anxiety about the risks of ART treatment among some infertile couples (Gourounti, 2016; Hammarberg et al., 2008), especially with regard to the survival of the fetus and early parenting difficulties (Hammarberg et al., 2008). Several studies have suggested that psychological distress during pregnancy has a negative effect on perinatal outcomes (Fransson et al., 2011; Lederman et al., 2004; Meng et al., 2012; Mulder et al., 2002; Rahman et al., 2007; Straub et al., 2012). In addition, based on the fetal programming hypotheses, some researchers have suggested that depression or anxiety during pregnancy might disturb the behavioural and emotional development of children (Field, 2011; O'Connor et al., 2003, 2005; Sharp et al., 2015).

There is evidence that the experience of undergoing ART treatment is stressful for both women and men (Freeman et al., 1985; Hjelmstedt et al., 2003; Monti et al., 2009, 2015). ART treatment was shown to be associated with maternal depression during late pregnancy and early parenthood (Monti et al., 2009), and the number of previous ART cycles was reported to be the strongest predictor of maternal depressive symptoms in the early postpartum period (Monti et al., 2015). The most important psychological determinant of reactions of couples during IVF was suggested to be the uncertainty of treatment procedures (Boivin et al., 1998). Spouses appeared to be equally sensitive to this uncertainty, and responded to it with ambivalent feelings involving emotional distress (Boivin et al., 1998).

On the other hand, several small-scale studies in Western countries have reported inconsistent findings in parents after a successful ART pregnancy (Colpin and Soenen, 2002; Fisher et al., 2008; Gibson et al., 2000; Golombok et al., 1995; Hjelmstedt et al., 2003; Jongbloed-Pereboom et al., 2012). Some studies reported that such couples were more anxious about losing the pregnancy than those with spontaneous conception (Hjelmstedt et al., 2003). Other studies

reported that very few women who had received ART treatment had clinically significant mood disturbance in late pregnancy (Fisher et al., 2008), and that the quality of parenting in families with a child conceived by ART was superior to that shown by families with a naturally conceived child (Golombok et al., 1995). However, some reports have suggested that there are no differences in mental distress during parenting between women who conceive via ART and those who do so spontaneously (Colpin and Soenen, 2002; Gibson et al., 2000), and ART treatment was not found to be associated with parental anxiety 1 year after childbirth (Jongbloed-Pereboom et al., 2012). These findings are, however, difficult to compare with each other since there is a great diversity between studies in terms of sample size, nationality, confounders, statistical analyses and evaluation methodology of psychological distress (e.g. assessment of timing of distress).

Since ART treatment is very expensive, it sometimes imposes a considerable economic burden on infertile couples (Bitler and Schmidt, 2012). In addition, they need a certain amount of education and knowledge to understand its efficacy and demerits. Interestingly, a Norwegian birth cohort study (Nilsen et al., 2013) reported that high socio-economic status and ART treatment were associated with first-time fathers of advanced age. Thus, societal characteristics related to ART treatment may somehow mediate the relationship between ART and emotional distress among parents undergoing the procedures. Although such societal characteristics are likely to be affected by cultural background, epidemiological evidence on non-Caucasian populations is very scarce as the majority of previous epidemiological studies have been conducted in Western countries. Growing evidence indicates a suite of generalized differences in attentional and cognitive processing, as well as emotion expression, between the Japanese and Westerners (Kuwabara and Smith, 2012; Uchida et al., 2009). For example, emotions are understood as between people in the Japanese context, whereas in the Western context, they are understood as primarily within people (Uchida et al., 2009). Thus, psychological distress related to ART treatment may be experienced differently by Japanese couples compared with Western couples.

Summarizing the previous findings, while mothers receiving ART treatment are likely to suffer from pregnancy-specific anxiety, the evidence regarding the association between maternal psychological distress during pregnancy and ART treatment are inconclusive even in Western populations, especially for findings relating to general anxiety levels, which may be inconclusive due to methodological limitations and differences between studies (Gourounti, 2016). For example, the majority of previous studies did not clarify

whether psychological assessment was carried out before, during or after pregnancy (Gourounti, 2016). These methodological limitations might be resolved, at least partially, by large-scale epidemiological studies.

The Japan Environment and Children's Study (JECS) is a large, nationwide longitudinal birth genome-cohort study funded by the Ministry of the Environment of Japan, with approximately 100,000 participants (Kawamoto et al., 2014). The present study aimed to evaluate the association between parental psychological distress, including mild depression and anxiety, in infertile couples receiving ART treatment compared with those receiving non-ART treatment (ovulatory induction and assisted insemination by husband [AIH]), and fertile couples who conceived spontaneously. This was done using longitudinal data obtained during the first trimester (T1) and the second/third trimester (T2) of the pregnancy. Although previous findings were inconsistent, it was hypothesized that Japanese couples who receive ART treatment would have more psychological distress than those who conceive spontaneously, since undergoing ART treatment has been reported to be a psychological burden for infertile Japanese couples in several published reports (Hayashitani and Suzui, 2009; Mori, 2012; Mori et al., 1997; Sasaki, 2014). To the authors' knowledge, this is the first epidemiological study regarding the association between ART treatment and parental distress in a non-Caucasian population.

Materials and methods

Study participants

The details of the JECS recruitment and sampling strategy, as well as data collection procedures, are reported elsewhere (Kawamoto et al., 2014). JECS aims to evaluate the effects of environmental factors on children's health and development from early pregnancy until their 13th birthday. Recruitment was performed in 15 regions of Japan by regional unit centres from January 2011 to March 2014. The present study is based on the data set 'jecs-ag-ai-20131008', which was released in October 2013. In total, 10,228 pregnant women (fetal records) were analysed in this study. The pregnant women were first recruited to participate in JECS when they were in T1, and were asked to provide written informed consent for the study. Fathers were also recruited in the same period. The next questionnaire study was conducted in T2. In the present investigation, the study population consisted of 10,228 pregnant women (fetal records) (Fig. 1), 723 of whom were excluded because of multiple births or lack of information regarding ART treatment ($n = 219$); a history of schizophrenia, cancer or stroke ($n = 132$); miscarriage or stillbirth during the period ($n = 113$); and non-response to the T1 questionnaire ($n = 259$). As the current data were collected per embryo, duplicate data from parents undergoing higher-order pregnancies were

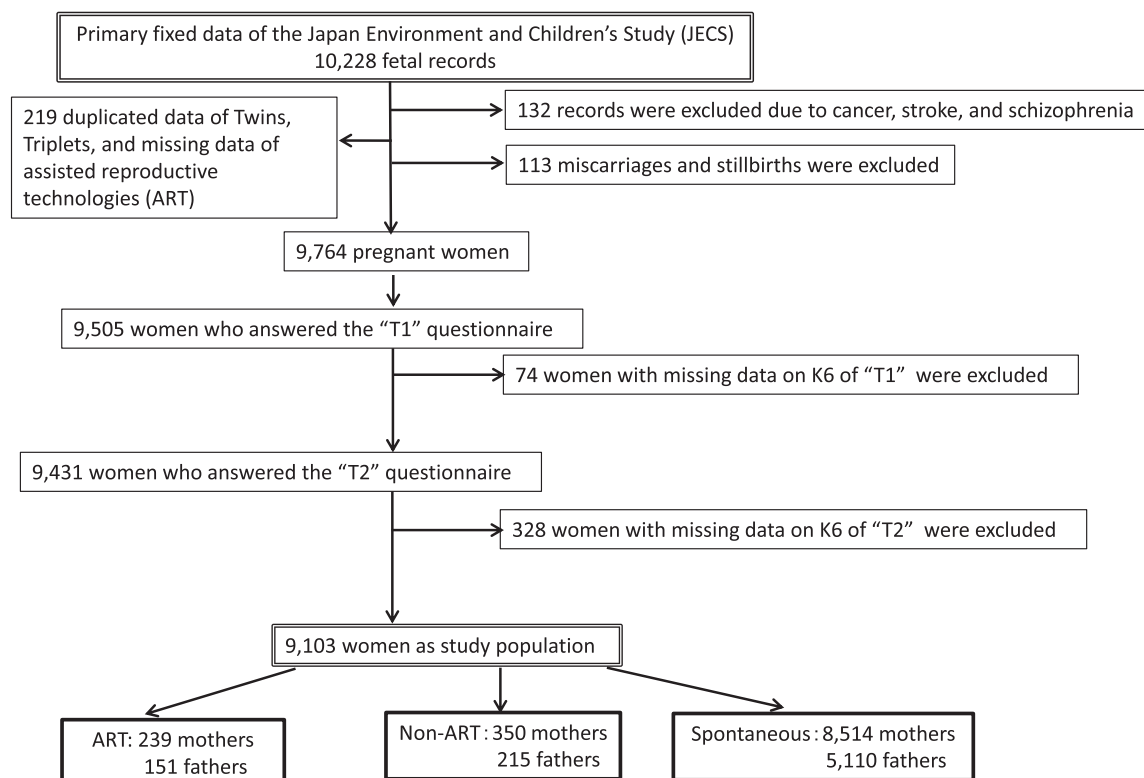


Fig. 1 Flowchart to identify the study population. Of the 9764 pregnant women, those with serious diseases or a history of miscarriage or stillbirth were excluded to leave 9505 women in the first trimester survey (T1 questionnaire). After further excluding those with missing data on depression in the second/third trimester survey (T2 questionnaire), 9103 women remained as the study population. ART, assisted reproductive technology; K6, Kessler Six-item Psychological Distress scale. Fig. 1.

excluded. As the association between ART treatment and distress in the context of multiple births is of considerable interest, this matter is the subject of a forthcoming study based on a nationwide sample (the present preliminary study is based on data from one regional unit and has a relatively small sample size, especially for multiple births). Mothers with a history of cancer were excluded since they were considered to have more severe depressive or anxiety symptoms compared with those without such a history, regardless of whether or not they received ART treatment.

Thus, data were collected on a total of 9505 women. After excluding another 402 mothers whose distress scores were missing, the subjects were classified into three groups: a group who received ART treatment (IVF or ICSI) (239 pregnant women and 151 fathers); a group who received non-ART treatment (ovulatory induction and AIH) (350 pregnant women and 215 fathers); and a group who conceived spontaneously (8514 mothers and 5110 fathers). The proportions of missing data for the distress scale did not differ significantly between the three groups ($P = 0.51$ for mothers and 0.63 for fathers), indicating that there was no significant bias caused by missing values. For the analysis of fathers alone, a total of 5597 subjects were eligible due to differences in missing values for the distress score between the couples. The three groups were further divided into primipara and multipara subgroups.

In Japan, only ovulatory induction is covered by the public health insurance system, while AIH and ART treatment are covered by private health insurance. Therefore, if couples who seek ART treatment do not have private health insurance, they must cover the high cost of treatment themselves.

Data on parental and child health, as well as basic characteristics, were collected using medical records and self-administered questionnaires. The data collection was mainly focused on mothers, including details about past illnesses, current pregnancy and delivery complications, delivery mode, neonatal abnormalities, feelings about the current pregnancy (assessed by one simple question, 'how did you feel when you became aware of your current pregnancy?'), and their relationship with their husband. Information on socio-economic factors (e.g. education and family income) and daily habits (e.g. drinking and smoking), as well as subjective health condition [assessed by the Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8 score)], was obtained for both mothers and fathers. This study was approved by the Ethics Committee of the National Institute for Environmental Studies, the core centre of JECS. Written informed consent was obtained from all participants.

Assessment of psychological distress

Psychological distress during pregnancy was measured using the Kessler Six-item Psychological Distress (K6) scale (Kessler et al., 2002, 2003). A Japanese version of the K6 scale was developed recently using the standard back-translation method, and shown to have excellent reliability and validity as a tool for mental health assessment (Furukawa et al., 2008; Nishi et al., 2012; Sakurai et al., 2011). The K6 scale consists of six questions that assess non-specific psychological

distress (depressive moods and anxiety) on a five-point scale ranging from 0 to 4. The sum of the scores for the six items, ranging from 0 to 24, is used to indicate the degree of psychological distress. A cut-off score of 5 is used to identify cases of depression and anxiety, including mild depression. This definition is based on previous evidence collected in Japan (Sakurai et al., 2011). The K6 scale was chosen for JECS as it has only six items, so it is not a burden to complete. A K6 score ≥ 5 at both T1 and T2 was defined as persistent distress.

Basic characteristics

The basic characteristics of the study subjects who participated in the T1 survey are summarized in Table 1. Information on age, marital status, feelings toward the current pregnancy, past history of mental illness, maternal smoking and drinking, and the K6 questionnaire was obtained in T1. In addition, information about family income, couple's educational level, quality of couple's relationship, stressful life events and the K6 questionnaire were obtained in T2. Comorbidities during pregnancy and delivery as well as neonatal health were checked by doctors using medical records.

Low family income, defined by the annual revenue of the household, was categorized as an annual income of 4,000,000 Japanese yen or less. A low educational level was defined by the highest academic background, and categorized as graduating from high school or less. A past history of mental illness included depression, anxiety disorder, schizophrenia and somatoform autonomic dysfunction suffered before pregnancy. These disorders were ascertained by self-administered questionnaire that included items regarding history of such disorders. If the participants with a past history or under treatment for such disorders checked these items, they were regarded as having a history of such mental disorders. 'Not married' was defined as never married, divorced or bereaved. Stressful life events included miscellaneous events such as death or illness of family members, debt, job loss or the death of a friend.

Data analysis

Analyses regarding categorical and continuous variables were conducted using the chi-squared test or analysis of variance (ANOVA), respectively. The K6 scores of those who conceived following infertility treatment (ART and non-ART) and those who achieved spontaneous pregnancy were compared separately for primipara and multipara status by one-way ANOVA followed by the multiple-comparison Scheffe test.

The association between distress during pregnancy and ART treatment was evaluated, and odds ratios were calculated using multivariate logistic regression analyses. In two models (1 and 2) of multivariate logistic regression analysis, the dependent variable was psychological distress, defined as a K6 score ≥ 5 . Model 1 was adjusted for age alone, as shown in Table 1. In Model 2, further adjustment was made for all selected basic characteristics: maternal/paternal age, maternal history of mental disorders (depression, anxiety, somatoform autonomic dysfunction), autoimmune diseases (collagenosis, systemic lupus erythematosus, rheumatism, other autoimmune and immune diseases), endocrine diseases

Table 1 Characteristics of the couples who conceived following assisted reproductive technology (ART) treatment, non-ART treatment and spontaneously.

Characteristic	ART ^a (n = 249)	Non-ART ^b (n = 370)	Spontaneous (n = 8886)
Mothers	%	%	%
Age (years) (SD)	36.2 (3.9)	33.0 (4.0)	30.9 (5.0)
Primipara	48.4	40.9	30.2
Education: high school or less	23.6	21.9	37.7
Annual income ≤4,000,000 Japanese yen	22.9	30.3	42.2
Not married ^c	0.4	0.3	4.5
Three or fewer family members	84.7	84.6	63.7
Current smoking ^d	3.2	9.8	19.9
Current drinking	9.2	8.7	9.9
Stressful life events	38.8	39.4	46.0
Not pleased at discovery of pregnancy	0.4	1.1	10.4
Insults from husband during pregnancy	7.9	8.2	14.3
Quarrelling between couple during pregnancy	0.0	0.6	1.5
Weight loss after pregnancy	18.8	27.0	20.1
Poor physical health ^e	76.2	75.1	71.6
Complications during pregnancy	19.3	15.8	12.4
Abnormal delivery	56.2	50.1	44.1
Neonatal physical abnormality	10.1	5.9	6.5
Fathers			
Age (years) (SD)	38.0 (5.3)	34.8 (5.5)	32.8 (5.8)
Education: high school or less	33.1	31.4	46.4
Poor physical health ^e	40.3	28.1	33.9
History of maternal disorders before pregnancy			
Depression	0.8	3.2	2.9
Somatiform autonomic dysfunction	4.0	5.1	3.6
Anxiety disorders	2.0	3.5	2.6
Autoimmune diseases	1.6	1.4	0.8
Endocrine diseases	6.8	4.1	2.5
Musculoskeletal diseases	4.8	2.2	2.4

SD, standard deviation.

The values are percentages unless otherwise specified. Those with missing values were excluded.

^a In-vitro fertilization or intracytoplasmic sperm injection.

^b Ovulatory induction or artificial fertilization.

^c Never married, divorced or bereaved.

^d Smoking at present or ceased smoking on discovery of pregnancy.

^e SF-8 score ≤50.

(type I and II diabetes mellitus, gestational diabetes, hyperand hypothyroidism, other endocrine diseases), musculoskeletal diseases (congenital dislocation of the hip, scoliosis, other musculoskeletal disorders), feelings on discovery of pregnancy, parental education, economic status, maternal smoking and drinking, maternal/paternal subjective physical health, comorbidity during pregnancy and delivery, neonatal health, weight change due to pregnancy, and discord in the husband–wife relationship. Although neonatal health and maternal weight change due to pregnancy may be related to postpartum depression, they were also adjusted for as the combined status of ART treatment and depression during pregnancy was considered to affect these factors. These factors were selected since they could be regarded as potentially confounding factors between ART treatment and parental psychological distress during pregnancy. They were included in the regression models as indicator variables representing categories of such factors as shown in Table 1. Regarding maternal history of disorders, each disorder was

included in the model as a dichotomous categorical variable (present or absent). These multivariate analyses were conducted separately for primipara and multipara status. Missing values of those covariates were also included in the model by creating categories of such data to prevent a decrease in number. All analyses were performed using SAS Version 9.4 (SAS Inc., Cary, NC, USA). A two-sided $P < 0.05$ was regarded as statistically significant.

Results

Demographic and basic characteristics

The characteristics of the subjects who conceived following ART treatment, non-ART treatment or spontaneously are presented in Table 1. At the time of the T1 examination, the mean age [standard deviation (SD)] of the women who received ART treatment was higher than that for women who

conceived spontaneously. The same is true for their male partners. In the group of pregnant women who underwent ART treatment, the maternal and paternal education levels and income were higher than in the spontaneous pregnancy group. In addition, the pregnant women who received ART treatment were more likely to be married, and less likely to have suffered from stressful events such as the death of their parents. The physical health conditions of both mothers and fathers were worse in the group of pregnant women who received ART treatment than in the other groups, as assessed by the SF-8 score. In addition, there were more complications during pregnancy, abnormal deliveries and neonatal physical abnormalities in the group of pregnant women who underwent ART treatment. In this group, the mothers were also more likely to suffer from endocrine diseases and musculoskeletal disorders. Since the variables listed in Table 1 were selected as potential confounders and not true random variables, *P*-values regarding the statistical differences of these factors between the three groups are not provided.

Associations between parental distress during pregnancy and ART treatment

In multivariate analysis, 402 mothers were excluded due to missing values for the K6 score, as mentioned above (Fig. 1). The results of multivariate logistic regression analysis showed that ART and non-ART treatments were significantly or marginally significantly associated with a lower risk of psychological distress among mothers compared with spontaneous pregnancy (Table 2). This tendency was apparent for ART treatment in multipara mothers and non-ART treatment in primipara mothers. However, after adjustment for all selected background characteristics, the associations were no longer significant. Likewise, age-adjusted analysis revealed that ART and non-ART treatments were significantly associated with a reduced risk of psychological distress in fathers. Again, however, they were no longer significantly associated with the decreased risk of distress after adjustment for baseline characteristics, except that non-ART treatment remained significant (Table 3).

Table 2 Association between maternal psychological distress^a and assisted reproductive technology (ART) treatment.

	T1 (n = 9103)	T2 (n = 9103)	T1 + T2 (n = 6968) ^b	T1 or T2 (n = 9103) ^c
Age-adjusted				
Spontaneous	1.00	1.00	1.00	1.00
Non-ART ^d	0.95 (0.75–1.20)	0.85 (0.66–1.09)	0.84 (0.62–1.13)	0.93 (0.75–1.16)
ART ^e	0.81 (0.60–1.09)	0.72 (0.52–0.99)	0.55 (0.36–0.86)	0.88 (0.67–1.15)
Fully adjusted ^f				
Spontaneous	1.00	1.00	1.00	1.00
Non-ART	1.12 (0.88–1.44)	1.05 (0.81–1.36)	1.10 (0.79–1.53)	1.11 (0.88–1.40)
ART	1.03 (0.75–1.40)	0.94 (0.67–1.31)	0.79 (0.49–1.26)	1.13 (0.85–1.50)
Primipara age-adjusted				
Spontaneous	1.00	1.00	1.00	1.00
Non-ART	0.70 (0.48–1.03)	0.68 (0.45–1.02)	0.59 (0.35–0.97)	0.69 (0.48–0.99)
ART	0.86 (0.56–1.33)	0.73 (0.46–1.17)	0.66 (0.36–1.19)	0.87 (0.58–1.29)
Primipara fully adjusted ^f				
Spontaneous	1.00	1.00	1.00	1.00
Non-ART	0.91 (0.60–1.37)	0.87 (0.56–1.35)	0.82 (0.46–1.44)	0.90 (0.61–1.23)
ART	1.13 (0.72–1.78)	0.95 (0.58–1.55)	0.99 (0.51–1.91)	1.15 (0.75–1.75)
Multipara age-adjusted				
Spontaneous	1.00	1.00	1.00	1.00
Non-ART	1.12 (0.84–1.51)	0.97 (0.71–1.32)	1.01 (0.69–1.48)	1.11 (0.84–1.46)
ART	0.75 (0.49–1.15)	0.69 (0.44–1.08)	0.46 (0.24–0.89)	0.86 (0.59–1.26)
Multipara fully adjusted ^f				
Spontaneous	1.00	1.00	1.00	1.00
Non-ART	1.28 (0.94–1.75)	1.16 (0.84–1.61)	1.34 (0.88–2.02)	1.26 (0.93–1.70)
ART	0.93 (0.60–1.45)	0.90 (0.56–1.44)	0.63 (0.31–1.27)	1.10 (0.74–1.64)

T1, first trimester; T2, second/third trimester.

Values are odds ratio (95% confidence interval).

Bold typeface indicates a statistically significant association.

^a Defined as K6 score ≥ 5 . Controls=K6 score ≤ 4 in both T1 and T2.

^b Persistent distress=K6 score ≥ 5 in both T1 and T2; non-persistent distress=K6 score ≥ 5 in either T1 or T2.

^c Persistent and non-persistent distress combined.

^d Ovulatory induction or artificial fertilization.

^e In-vitro fertilization or intracytoplasmic sperm injection.

^f Adjusted for maternal age, maternal history of mental disorders, autoimmune diseases, endocrine diseases, musculoskeletal diseases, maternal feeling on discovery of pregnancy, parental education, economic status, maternal smoking and drinking, maternal subjective physical health, comorbidity during pregnancy and delivery, neonatal health, weight change due to pregnancy, and discord in husband–wife relationship.

Table 3 Association between paternal psychological distress and assisted reproductive technology (ART) treatment.

	Age-adjusted odds ratio (95% CI) (distress ^c vs controls, n = 5597)	Fully adjusted ^d odds ratio (95% CI) (distress vs controls, n = 5597)
All		
Spontaneous	1.00	1.00
Non-ART ^a	0.59 (0.40–0.86)	0.66 (0.45–0.97)
ART ^b	0.67 (0.43–1.04)	0.71 (0.45–1.11)
Primipara		
Spontaneous	1.00	1.00
Non-ART	0.51 (0.28–0.95)	0.55 (0.29–1.04)
ART	0.69 (0.37–1.31)	0.72 (0.37–1.40)
Multipara		
Spontaneous	1.00	1.00
Non-ART	0.64 (0.40–1.04)	0.74 (0.45–1.22)
ART	0.64 (0.34–1.19)	0.69 (0.36–1.31)

CI, confidence interval.

Bold typeface indicates a statistically significant association.

^a Ovulatory induction or artificial fertilization.

^b In-vitro fertilization or intracytoplasmic sperm injection.

^c K6 score ≥ 5 .

^d Adjusted for paternal age, maternal history of mental disorders, autoimmune diseases, endocrine diseases, musculoskeletal diseases, maternal feeling on discovery of pregnancy, parental education, economic status, maternal smoking and drinking, paternal subjective physical health, comorbidity during pregnancy and delivery, neonatal health, weight change due to pregnancy, and discord in husband–wife relationship.

Highly distressed mothers among the group of pregnant women who received ART and non-ART treatments

While the majority of mothers who received ART and non-ART treatments reported less distress in both the T1 and T2 periods, a small number (10.0%, n = 24 for ART; 16.0%, n = 56 for non-ART) had persistent distress in both periods, which could continue to have negative psychological consequences. Therefore, the factors that differed between these women and those who received ART or non-ART treatment without distress in T1 and T2 were examined using chi-squared and Fisher's exact tests. This analysis found that persistent distress was highly associated with insults from the husband ($P = 0.0018$ for ART, 0.0047 for non-ART) (Tables 4 and 5, respectively). Stressful life events, complications during pregnancy and history of anxiety disorders were more prevalent among non-ART mothers with persistent distress. On the other hand, many factors were found to be significantly different between mothers with persistent distress and controls in the spontaneous pregnancy group. Mothers with persistent distress were more likely to be smokers, not pleased on discovery of pregnancy, not married, have lower educational background, have lower economic status, and have a poor relationship with their husband, including insults and quarrels (data not shown). These significant differences may be observed due to the large sample size.

Table 4 Comparison of parental factors between persistently distressed and non-distressed mothers who underwent assisted reproductive technology (ART) treatment.

Factor	Persistent distress ^a (n = 24)	Controls ^b (n = 152)	P-value
Demographic factors			
Maternal age (years) (SD)	35.2 (3.3)	36.4 (4.0)	0.17
Paternal age (years) (SD)	37.6 (5.9)	38.4 (5.6)	0.63
Maternal age ≥ 35 years	66.7	68.9	0.83
Paternal age ≥ 40 years	28.6	37.8	0.51
Age difference between couple ≥ 10 years	7.1	5.6	0.59 ^c
Primipara	58.3	48.0	0.35
Maternal education: high school or less	25.0	23.7	0.89
Paternal education: high school or less	29.2	34.9	0.58
Annual income $\leq 4,000,000$ Japanese yen	25.0	23.8	0.90
Not married ^d	4.2	0.0	0.14 ^c
Three or fewer family members	83.3	82.2	1.00
Personal factors			
Current maternal smoking ^e	0.0	4.0	1.00 ^c
Passive maternal smoking	37.5	39.7	0.84
Current maternal drinking	12.5	10.5	0.73 ^c
Stressful life events	45.8	32.9	0.26
Not pleased on discovery of pregnancy	0.0	0.7	1.00 ^c
Insults from husband	25.0	4.0	0.0018^c
Medical factors			
Poor maternal physical health ^f	83.3	73.5	0.30
Complications during pregnancy	30.4	15.9	0.14 ^c
Abnormal delivery	60.9	51.7	0.41
Neonatal physical abnormality	9.5	7.4	0.66 ^c
History of depression	4.2	0.0	0.14 ^c
History of somatoform autonomic dysfunction	12.5	3.3	0.08 ^c
History of anxiety disorders	4.2	2.0	0.45 ^c
History of autoimmune disease	0.0	1.3	1.00 ^c
History of endocrine diseases	4.2	7.2	1.00 ^c
History of musculoskeletal diseases	12.5	5.3	0.18 ^c

SD, standard deviation.

Values are percentages unless otherwise specified. Missing data were excluded from the analyses.

Bold typeface indicates a statistically significant difference.

^a K6 score ≥ 5 in both first and second/third trimesters.

^b K6 score ≤ 4 in both first and second/third trimesters.

^c Fisher's exact test.

^d Never married, divorced or bereaved.

^e Smoking at present or ceased smoking on discovery of pregnancy.

^f SG-8 score ≤ 50 .

The proportions of those with persistent distress among mothers with non-ART treatment and spontaneous pregnancy were significantly higher than for those who underwent ART

Table 5 Comparison of parental factors between persistently distressed and non-distressed mothers who underwent non-assisted reproductive technology (ART) treatment.

Factor	Persistent distress ^a (n=56)	Controls ^b (n=211)	P-value
Demographic factors			
Maternal age (years) (SD)	32.3 (3.9)	33.0 (4.1)	0.27
Paternal age (years) (SD)	33.6 (3.9)	34.9 (5.9)	0.13
Maternal age ≥ 35 years	34.6	37.3	0.70
Paternal age ≥ 40 years	6.1	18.3	0.08
Age difference between couple ≥ 10 years	0.0	4.6	0.60 ^c
Primipara	34.6	44.1	0.20
Maternal education: high school or less	19.6	20.5	0.89
Paternal education: high school or less	35.7	30.8	0.48
Annual income ≤ 4,000,000 Japanese yen	27.8	28.2	0.95
Three or fewer family members	82.1	85.7	0.51
Personal factors			
Current maternal smoking ^d	40.0	60.0	0.014
Passive maternal smoking	48.2	41.7	0.38
Current maternal drinking	12.5	10.0	0.58
Stressful life events	56.4	31.1	0.0005
Not pleased on discovery of pregnancy	1.8	1.0	0.51 ^c
Insults from husband	14.3	3.4	0.0047^c
Quarrelling between couple during pregnancy	1.8	0.5	0.38 ^c
Medical factors			
Poor maternal physical health ^e	80.4	72.1	0.21
Complications during pregnancy	28.9	13.5	0.008
Abnormal delivery	51.9	46.9	0.52
Neonatal physical abnormality	7.6	5.8	0.75 ^c
History of depression	3.6	1.9	0.61 ^c
History of somatoform autonomic dysfunction	7.1	4.3	0.48 ^c
History of anxiety disorders	10.7	2.4	0.013^c
History of autoimmune disease	3.6	1.0	0.19 ^c
History of endocrine diseases	7.1	3.8	0.28 ^c
History of musculoskeletal diseases	0.0	2.8	0.35 ^c

SD, standard deviation.

Values are percentages unless otherwise specified. Missing data were excluded from the analyses.

Bold typeface indicates a statistically significant difference.

^a K6 score ≥ 5 in both first and second/third trimesters.

^b K6 score ≤ 4 in both first and second/third trimesters.

^c Fisher's exact test.

^d Smoking at present or ceased smoking on discovery of pregnancy.

^e SG-8 score ≤ 50.

treatment (16% for non-ART, 18.9% for spontaneous pregnancy; $P = 0.0011$).

Severity and proportion of distress among mothers and fathers during pregnancy

Table 6 shows the mean K6 scores of subjects during pregnancy separately by primipara and multipara groups, and the proportion of subjects with psychological distress (K6 score ≥ 5). Overall, mothers had higher K6 scores than fathers, and the proportion of distress was also generally higher in mothers than in fathers. The highest proportion of distress was observed in mothers with primipara spontaneous pregnancies. Statistically significant differences between the three groups (i.e. those achieving pregnancy following ART treatment, non-ART treatment and spontaneously) were observed by ANOVA in all subgroup analyses, except that there were no significant differences between the groups for primipara fathers ($P = 0.23$). Multiple comparisons using the Scheffe test revealed significant differences between multipara mothers who underwent ART or non-ART treatment in T1, primipara spontaneous mothers and those who underwent ART treatment in T1, and multipara spontaneous mothers and those who underwent ART treatment in T2.

Discussion

The present study evaluated mental distress using the K6 scale in couples who achieved pregnancy following ART treatment, non-ART treatment or spontaneously. The majority of the mothers who had received ART treatment were less distressed than those in the spontaneous pregnancy group in both T1 and T2. This tendency to be less distressed was more apparent in multipara women who had undergone ART treatment. However, after controlling for selected basic characteristics, the apparent beneficial effect of ART treatment in reducing distress disappeared. No substantial associations were observed between ART treatment and maternal distress during pregnancy, consistent with other reports indicating that there were no differences between women who conceived following ART treatment and those with spontaneous pregnancies with regard to psychological distress (Colpin and Soenen, 2002; Gibson et al., 2000; Gressier et al., 2015). Although similar findings were observed for fathers, those who underwent non-ART treatment were least likely to be distressed, as shown by a significant odds ratio.

In spite of the poorer physical condition of the couples who underwent ART treatment, and contrary to the authors' expectations, ART treatment was associated with a somewhat lower risk of psychological distress. This result might be explained by the fact that ART treatment is now widely accepted as a common treatment in Japan, not only for infertile couples of reproductive age but also for those who marry late and desire a child. As mentioned previously, ART treatment alone is covered by private health insurance, and the associated counselling service is conducted by a specialized reproductive psychology counsellor, which may be very effective in reducing the risk of mental distress among parents. In addition, the majority of patients who

Table 6 Mean score on Kessler Six-item Psychological Distress (K6) scale and distribution of psychological distress (K6 score ≥ 5) among mothers and fathers during pregnancy.

Distress		K6 score (mean)	K6 score ≥ 5 (%)	
Mothers (T1)	Primipara	ART	2.91	27.6
		Non-ART	3.23	
		Spontaneous	3.85 ^a	
	Multipara	ART	2.75	22.0
		Non-ART	3.89 ^a	
		Spontaneous	3.55	
Mothers (T2)	Primipara	ART	2.72	21.6
		Non-ART	2.82	
		Spontaneous	3.48	
	Multipara	ART	2.52	20.5
		Non-ART	3.54	
		Spontaneous	3.48 ^a	
Fathers	Primipara	ART	2.33	16.7
		Non-ART	2.15	
		Spontaneous	2.71	
	Multipara	ART	1.77	14.1
		Non-ART	1.96	
		Spontaneous	2.67	

T1, first trimester; T2, second/third trimester; ART, assisted reproductive technology.

^a Scheffe test, <0.05 .

receive ART treatment might be less worried about safety aspects, as the perinatal outcomes for children born after ART treatment have improved greatly over the last 20 years (Henningsen et al., 2015). These facts indicate that ART treatment can be acceptable for infertile couples without any psychological resistance. Also, of course, it is expected that such couples would have very positive feelings about being pregnant after previously being unable to conceive.

On the other hand, this inverse association between ART treatment and distress diminished after controlling for selected variables, which indicates that the protective effects of ART treatment against distress might be mediated through such factors. For example, couples with high socio-economic status (e.g. a high educational background) might have less anxiety as they are more likely to study ART treatment and can better understand it than those with a low educational background. Furthermore, couples with poor subjective health may be more likely to be cared for by the ART counselling system mentioned above. Indeed, social support was shown to be negatively associated with distress in IVF patients (Rockliff et al., 2014). Meanwhile, it should be noted that infertile women showed a tendency towards anxiety and psychological distress (Gourounti et al., 2010; Rockliff et al., 2014; Verhaak et al., 2007). They reported high levels of psychological stress and a sense of isolation. In the current study, some ART and non-ART mothers reported being mentally distressed early in the pregnancy and remained distressed, and this was particularly the case in women receiving insults from their husbands, which indicates that this type of behaviour should be strictly avoided in couples who undergo treatment for infertility.

There was a gender difference in reported distress in the group of pregnant women who received ART treatment, with

women reporting more severe distress than men. This may be related to the closer physical relationship between the women and pregnancy, and the greater weight that society places on the role of women as mothers. Other studies have reported similar results (Boivin et al., 1998; El Kissi et al., 2013; Gibson et al., 2000; Hjelmsstedt et al., 2004). Associations between distress and ART treatment in fathers showed patterns similar to those of mothers. Although a marginally negative association was observed between ART treatment and distress in fathers, it diminished after controlling for selected variables, consistent with other reports finding no differences between ART and control fathers (Colpin and Soenen, 2002; Gibson et al., 2000). On the other hand, the negative association between non-ART treatment and distress in fathers remained significant even after adjusting for the selected factors. Although the reason is unclear, fathers, especially those who underwent non-ART treatment, would be relieved by a successful pregnancy. The smaller economic burden of non-ART treatment compared with ART treatment may partly explain this phenomenon since, in many cases, fathers are responsible for supporting the family financially. These findings indicate that further investigation is warranted to explain the differences between fathers who undergo ART and non-ART treatments. In addition, a few Swedish studies reported differences in psychological profiles between couples undergoing ART treatment (Johansson et al., 2010; Volgsten et al., 2010). Men with successful IVF were reported to have higher psychological general well-being, fewer signs of depression and more self-confidence than women in that group (Johansson et al., 2010). As Sweden has a highly developed welfare system, the economic burden related to ART treatment would be much lighter than in Japan.

Few studies have used the K6 scale to assess psychological distress during pregnancy. In a Japanese nationwide survey in 2013 (Ministry of Health, Labour and Welfare of Japan, 2013), 67.3% of normal Japanese citizens aged ≥ 12 years had K6 scores ≤ 4 , 18.0% had scores of 5–9, 7.2% had scores of 10–14, and 2.6% had scores ≥ 15 . In the present study, the K6 score showed a similar pattern, with 68.1% having K6 scores ≤ 4 , 23.5% having scores of 5–9, 6.7% having scores of 10–14, and 1.6% having scores ≥ 15 at T1. This suggests that the current sample is representative of the general population, and the K6 scale is suitable for large population studies. However, the use of this approach does make it more difficult to compare the results with those of previous studies due to the lack of such studies using the K6 scale, as mentioned below.

The number of babies born as a result of ART treatment will continue to increase in Japan and worldwide. Recently, advances in ART treatment include the use of surrogate mothers and host mothers. The former use their own eggs, while the latter use donor eggs or those of the intended mother. While these procedures are currently prohibited in Japan, a few infertile Japanese couples have used them abroad. It is not fully understood what additional societal pressures will result from such approaches. It will be essential for the resulting children to be followed-up as they progress through adolescence into adulthood, with an additional focus on the effects of parental psychological distress on the children themselves. Given the short- and longer-term consequences of prenatal psychological stress

and/or depression, there is great interest in how such mental distress affects these parents, and how this could affect their bonding with their children and parenting. Overall, the long-term mental health of couples after successful ART treatment has been shown to be good in Western studies (Sydsjö et al., 2015; Vikström et al., 2015). JECS is a large, nationwide longitudinal birth genome-cohort study with approximately 100,000 participants that aims to evaluate the effects of environmental chemicals on children's health and development from early pregnancy until their 13th birthday (Kawamoto et al., 2014). As such, this resource will also be of huge value for understanding the effects of parental distress in both spontaneous and ART pregnancies.

This study has some limitations. Firstly, the study collected little data before pregnancy, especially regarding mental state just before the pregnancy, and no information about the stress of the ART treatment itself. However, the proportion of those with a history of depression did not differ significantly between the three groups. Second, analysis of pregnancy complications was not possible because another paper had already described the situation in detail. As variables to be used in the research are under strict regulation of the JECS rules, detailed analyses of other variables, such as pregnancy complications, are not permitted, except in the case that such variables are used simply as covariates for adjustment. Furthermore, although the K6 scale was developed recently and is appropriate for use in large population studies, few reports have used it to assess psychological distress during pregnancy. Lastly, since timings of the psychological assessment in the previous studies have been inconsistent, current findings may not be simply comparable with previous findings.

In summary, this study found that parents who had undergone ART treatment did not report elevated psychological distress during a successful pregnancy in comparison with those who achieved spontaneous conception. Furthermore, these parents might be protected from such stress as a consequence of their greater maturity, or the enhanced support they received as part of the ART treatment. However, some mothers who had ART treatment continued to suffer from distress in both T1 and T2, which might impact the developmental and longer-term outcomes of their children. As such, a long-term follow-up study of the health of mothers and children after ART treatment was conducted, the results of which will be presented separately.

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Appendix A

The members of the Japan Environment and Children's Study (JECS) in 2015 were as follows: Toshihiro Kawamoto

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