

# Spontaneous Conception in a 50-year Old Woman after Giving up In-Vitro-Fertilization (IVF) Treatments: Involvement of the Psychological Relief in Successful Pregnancy

Hidehiko MATSUBAYASHI, Katsuhiko IWASAKI, Takashi HOSAKA\*,  
Yoko SUGIYAMA\*, Takahiro SUZUKI, Shun-ichiro IZUMI, and Tsunehisa MAKINO

*Department of Obstetrics and Gynecology, Center for Growth and Reproductive Medicine and  
\*Department of Psychiatry and Behavioral Science, Center for Internal Medicine,  
Tokai University School of Medicine*

(Received November 8, 2002; Accepted January 7, 2003)

A healthy woman, married at age 45, hoped to have their child without delay. She and her husband subsequently decided to pursue in-vitro-fertilization and embryo transfer (IVF-ET). In the succeeding year, ET was performed twice from four oocyte retrieval attempts, which represented six ovarian stimulation cycles. Pregnancy was not achieved. Because of her poor responses to ovarian stimulation, inferior oocyte grading and prohibition of donor oocyte usage in Japan, the couple decided to discontinue further IVF treatment at age 48 years, 10 months. One and one-half years later, at age 50 years, 3 months she presented to our clinic eight weeks pregnant. At term she delivered vaginally a 2740 g healthy infant at 38 weeks gestation; Apgar scores were 9 and 10. During her pregnancy, she willingly participated in our questionnaire designed to provide information about her psychological well-being during the past three years. During the time spanning her treatment for infertility, anxiety, depression, irritability, fatigue and grief were revealed to coexist with her high hopes of having a child. After termination of infertility treatments these adverse psychological findings were markedly lessened and her vigour was restored. Stopping infertility treatment might be a viable alternative for achieving pregnancy in similarly psychologically-challenged infertile women.

**Key words :** aging, distress, IVF-ET, infertility, Japan.

## INTRODUCTION

Advancing female age is a well-documented problem in achieving a successful pregnancy [1, 2]. By using donated oocytes, women have become pregnant in their late 50's and older [3, 4]. Thus, it appears that the age-related decline in fertility is due primarily to oocyte aging [5, 6]. In Japan, however, oocyte donation is prohibited. Therefore, infertility treatment ends with menopause or by anovulation, the latter including premature ovarian failure. When this occurs, most couples discontinue further treatments, however, some couples chose to go to other countries to seek donor oocytes and undergo

additional IVF attempts. As a consequence, infertile Japanese women view aging with apprehension, especially with regard to their oocyte quality and/or their potential to remain eligible for continuation of infertility treatments. Therefore, most Japanese Gynecologist believe and advise that women over 40 years old who want to have their children should choose IVF-ET in earlier convenience. Once IVF-ET was performed, however, it is difficult to cease IVF-ET, because we don't have other option to give such older women.

To our knowledge, the oldest spontaneous conception occurred in a 60-year old woman in 1998, which was reported in a UK news-

paper. We now report a spontaneous conception in a 50-year old woman 1.5 years after withdrawing from IVF treatment because of inferior oocyte grading and poor oocyte retrieval. We believe that our patient represents the eldest example on record of a spontaneous conception and delivery after cessation of IVF treatment. This case suggests that only continuation of IVF treatment may not be appropriate for such older women and that quitting IVF treatment does not always mean giving up being pregnant, because psychological factor cannot be excluded.

### CASE REPORT

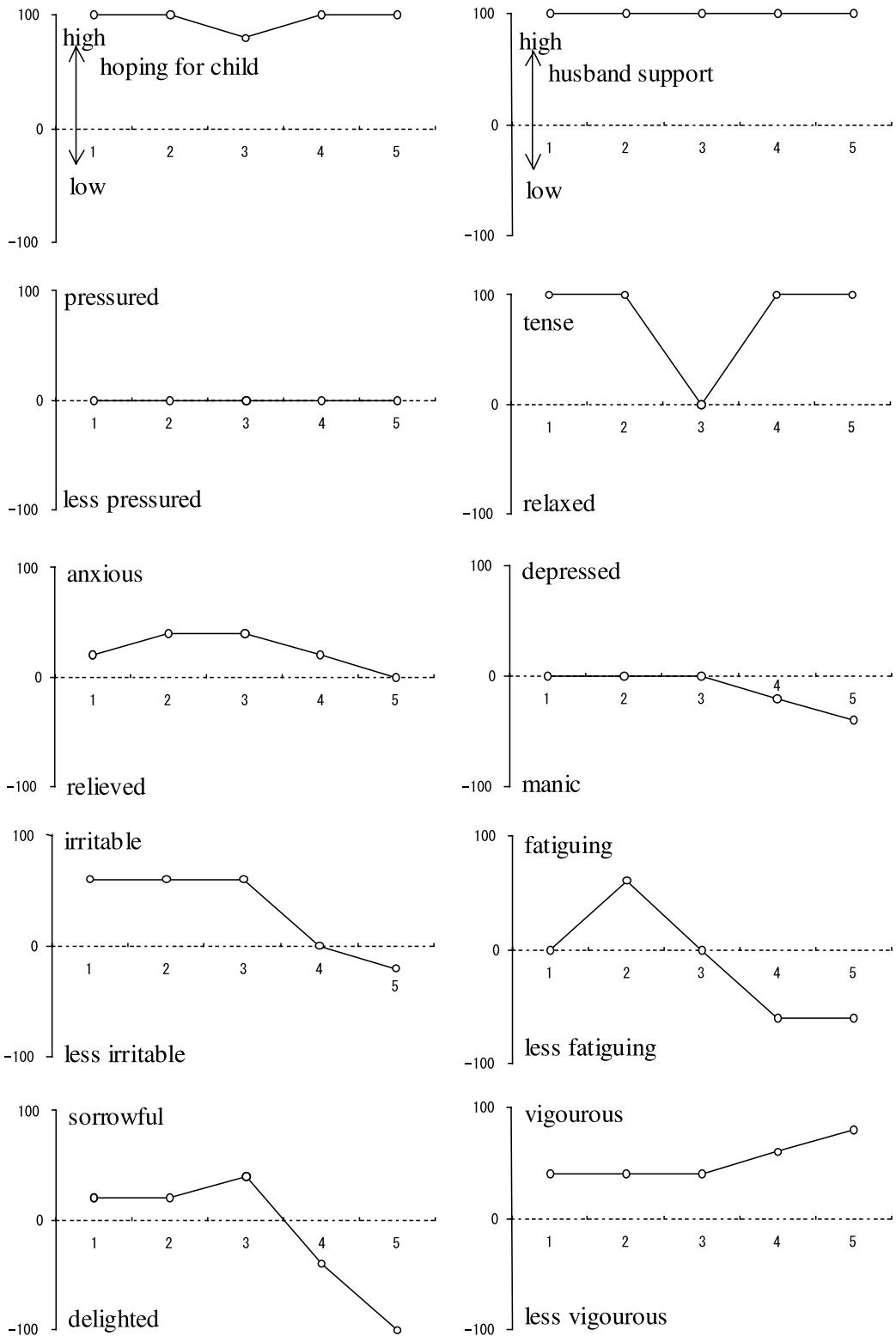
A healthy, nulligravid woman married at age 45 experienced two early pregnancy losses at ages 46 and 47. The first loss was at eight weeks (positive fetal heart tones) and the second loss was at seven weeks (blighted ovum) of gestation. After her second miscarriage, at 47 years 3 months of age, she presented to our infertility clinic. She and her husband hoped to have their child without delay. Her husband's semen analyses showed slightly asthenozoospermia (40-45 % but total motile sperm was normal ( $20-28 \times 10^6$ ). She opted to circumvent our routine work-up for infertility except for hormonal tests because she had had two documented pregnancies, and, in view of her age, she did not want to undergo the usual tests for recurrent pregnancy loss. Her menstrual cycle historically had been 30 days, but it was irregular during the past 2 years (20-60 days cycle). Ultrasound examination revealed her uterus and both ovaries to be unremarkable. Her basal follicle-stimulating hormone (FSH) level was normal (3.4 IU/L), and she did not have hyperprolactinemia or a luteal phase defect. She didn't have psychiatric disorders.

During first 4 months, she was advised to have coitus at the day of ovulation monitored by ultrasound, but not pregnant. In succeeding 3 months, intrauterine insemination with her husband's sperm was performed in view of asthenozoospermia, but failed to conceive. She and her husband did request IVF-ET. Their rationale for this choice was that IVF-ET procedure had the highest pregnancy success rate among infertility treatments, and that the residual oocytes might not be much in her age. A clomiphene-citrate-challenge test was performed that showed a good response for FSH (3.4 IU/L

to 24.7 IU/L). Since there was no significant difference between clomiphene citrate plus gonadotropins and gonadotropin-releasing hormone (GnRH) agonist combined with gonadotropins for patients over 40 in our institute, the former was selected for ovarian stimulation. The first attempt for IVF resulted in no oocyte retrieval from either ovary. In the second and third oocyte retrieval attempts, embryo transfers with Veeck-graded 3 and 2 embryos respectively (only one embryo per each cycle) were unsuccessful. After these three consecutive attempts, she became anovulatory. Two cycles of hormone replacement therapy were instituted, but the fourth and fifth oocyte recovery attempts were abandoned as no growing follicles were detected. Her basal FSH level was 41.6 IU/L at age 48 years, 6 months. Another two cycles of hormone replacement therapy were performed to obtain reduced FSH levels (8.7 IU/L). To maintain the lower levels of FSH for the sixth retrieval attempt, a long-GnRH agonist protocol combined with gonadotropins was performed, but only one degenerated oocyte was retrieved. In summary, no pregnancy was achieved after two embryo transfers were performed as a result of four oocyte retrieval attempts and six ovarian stimulation cycles.

After frank discussions about future expectations regarding additional infertility treatments, she and her husband concluded that they should cease further IVF treatment. Their decision was based upon the wife's poor response to ovarian stimulation, inferior-grade oocytes and prohibition of donor oocytes usage in Japan. At age 48 years, 10 months she and her husband stopped infertility clinic visits and she quit monitoring her basal body temperature.

One and one half years later at age 50 years, 3 months, she appeared at our clinic to say she might be pregnant. Her menstrual cycle was also irregular (20-60 days cycle). At that time, her pregnancy was eight weeks gestation and she complained of a slight emesis. She was afraid of a fetal anomaly because she had taken several drugs for a common cold. We discussed the risk of fetal anomalies resulting from the drugs and her additional risks due to her age. After contemplating pregnancy termination, the couple chose to have the baby. Between 10 and 14 weeks of gestation she was admitted



**Fig. 1** Assessment of patient feelings by using our questionnaire with visual analog scale. 1; before visiting our infertility clinic, 2; during infertility treatments, 3; after quitting infertility treatments, 4; two months before conception, 5; surrounding conception.

to our hospital for a threatened abortion and hyperemesis gravidarum. Her thyroid function was normal. The couple declined amniocentesis because they had decided to have this baby regardless of the outcome. After that, her pregnancy was uneventful. She was delivered at 38 weeks gestation of a 2740 g (6 lb.) infant with Apgar scores of 9 and 10. The infant was healthy without any abnormalities.

While pregnant, she agreed to participate in our questionnaire with visual analogue scales (VAS) designed to ascertain retrospective information about her psychological well-being for the past three years (Appendix I). The aim of this questionnaire is to see changing of feeling with this period, which is not absolute but relative. Her responses revealed that her aspirations for having children had continued unabated during this period (Fig. 1). Her husband remained supportive throughout this period. Feelings of pressure were scored as consistently neutral. Tension scores were decreased temporally when her infertility treatments were discontinued, but reappeared before she became pregnant. Anxiety, depression, irritability, fatigue and grief were markedly reduced after stopping her infertility treatments and her vigor was restored to normal values.

## DISCUSSION

The patient in our case report decided to give up IVF treatments because of inadequate responses to ovarian stimulation and poor-quality oocytes. She subsequently conceived spontaneously and we observed her conception to coincide with her psychological assessment of relief after quitting infertility treatment.

Spontaneous conception subsequent to the birth of infants conceived through IVF-ET has been reported to approximate 20 % [7, 8]. Perhaps this 20 % might not have needed IVF treatment in the past, or alternatively, the successful delivery of an infant might improve the environment for an unaided pregnancy. Those authors speculated that the most likely cause of spontaneous conception in these women is the relief of stress, but it was never documented by evaluation in their papers [7, 8]. Other report observed that spontaneous pregnancies occurred with 11 % per 5 years even in women who had to perform intracytoplasmic sperm injection

(ICSI) treatment to get fertilized eggs (i.e., no fertilization without ICSI) [9]. We also have noticed that some unexplained infertile women become pregnant spontaneously after geographic relocations, changing or quitting jobs, transferring to another clinic, as well as discontinuing their infertility treatments (unpublished observations). Together these findings suggest that psychological factors are of concern in certain infertile patients.

The underlying reasons responsible for these spontaneous pregnancies in these “infertile” patients awaits closer scrutiny as assessments of psychological well-being cannot be made for women who have not been tested or followed. We can't follow women who give up to have a child, because they have no reason to come to infertility clinic. Clearly, many questionnaires used for psychological evaluations do not inquire about retrospective information. To overcome this deficit, we tried to develop an original questionnaire with VAS (Appendix I). Our questionnaire measures the intensity of mood, which may be called as Visual Analogue Mood Scale (VAMS). In terms of the reliability of VAS or VAMS, test re-test reliability and inter-rater reliability has been reported in the same individual [10]. There were very high correlations between the initial rating and recall rating [10]. The accuracy of VAS recalling for more than 2 years, however, is still uncertain. The feature of our questionnaires is that we put a series of VAS (5 time points) together to reduce retrospective bias, which makes relative changes clear during answering. It might be said that VAS should be tested during the pilot study [10]. Since there will be no progress in this field without this types of questionnaires, we think that it can provide valuable and useful information in this situation.

This woman in our case report may not need IVF treatment, because she had two pregnancies before treatment. She subsequently, however, became infertile after coming to our clinic without conception for 20 months. She and her husband had strong hope to perform IVF treatment to achieve pregnancy without delay, but this choice might be wrong. She might have her own child earlier without infertility treatment.

It is known that infertility treatment alone is stressful [11, 12], and failure to conceive

can compound this condition and lead to depression [13], which can be recognized and managed [14, 15]. Although most studies have suggested that infertility or infertility treatment is a source of psychological distress, other recent studies state that stress may be a causal factor for infertility. Pre-existing psychological features, for examples, anxiety, depression, and negative emotional states are independently related to IVF-ET failure [16, 17]. Indeed, anxiety is correlated with uterine contraction frequency at the time of ET, which may induce implantation failure [18]. Another possible explanation is the physiological link between hormonal changes and psychological states. Anxiety induces hyperprolactinemia resulting in failure to conceive [19, 20]. Similarly, emotional stress caused by either anxiety or depression can induce changes in prolactin, cortisol and testosterone [21, 22]. There are reports appearing that reduced scores of anxiety and/or depression are related to successful conception [23, 24], and that counseling has been reported to be effective in reducing anxiety and depression [25] and result in successful conception [26, 27].

In conclusion, infertility or infertility treatment is a source of psychological distress, but this may be a causal factor for infertility at the same time. Most Japanese Gynecologist believe and advise that women over 40 years old who want to have their children should choose IVF-ET in earlier convenience. Once IVF-ET was performed, however, it is difficult to cease IVF-ET, because we don't have other option to give such older women. The psychological release seems to be observed in our patient after stopping infertility treatment followed by successful conception. This case suggests that simple continuation of IVF treatment may not be appropriate to achieve pregnant for such older women and that quitting IVF treatment does not always mean giving up being pregnant, because psychological factor cannot be excluded. Since studies assessing emotional well-being, infertility and fecundity have yet to be published for women who don't come to infertility clinic, we hope that this case report will stimulate others to explore this potential.

#### ACKNOWLEDGEMENT

This study was supported in part by a Project Research Grant, Tokai University

School of Medicine, Japan. We thank Dr. John A. McIntyre for reading and editing our manuscript.

#### REFERENCES

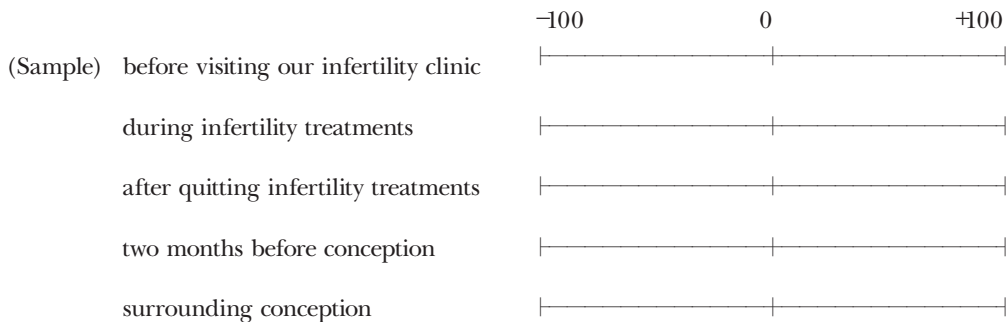
- 1) Stein ZA: A woman's age: childbearing and child rearing. *Am J Epidemiol* 121: 327-342, 1985.
- 2) Szamatowicz M, Grochowski D: Fertility and infertility in aging women. *Gynecol Endocrinol* 12: 407-413, 1998.
- 3) Borini A, Bafaro G, Violini F, Bianchi L, Casadio V, Flamigni C: Pregnancies in postmenopausal women over 50 years old in an oocyte donation program. *Fertil Steril* 63: 258-261, 1995.
- 4) Paulson RJ, Thornton MH, Francis MM, Salvador HS: Successful pregnancy in 63-year-old woman. *Fertil Steril* 67: 949-951, 1997.
- 5) Abdalla HI, Burton G, Kirkland A, Johnson MR, Leonard T, Brooks AA, Studd JW: Age, pregnancy and miscarriage: uterine versus ovarian factors. *Hum Reprod* 8: 1512-1517, 1993.
- 6) Sauer MV: Infertility and early pregnancy loss is largely due to oocyte aging, not uterine senescence, as demonstrated by oocyte donation. *Ann NY Acad Sci* 828: 166-174, 1997.
- 7) Hennelly B, Harrison RF, Kelly J, Jacob S, Barrett T: Spontaneous conception after a successful attempt at *in vitro* fertilization/intracytoplasmic sperm injection. *Fertil Steril* 73: 774-778, 2000.
- 8) Shimizu Y, Kodama H, Fukuda J, Murata M, Kumagai J, Tanaka T: Spontaneous conception after the birth of infants conceived through *in vitro* fertilization treatment. *Fertil Steril* 71: 35-39, 1999.
- 9) Osmanagaoglu K, Collins JA, Kolibianakis E, Tournaye H, Camus M: Spontaneous pregnancies in couples who discontinued intracytoplasmic sperm injection treatment: a 5-year follow-up study. *Fertil Steril* 78: 550-556, 2002.
- 10) McCormack HM, Horne DJ, Sheather S: Clinical applications of visual analogue scales: a critical review. *Psychol Med* 18: 1007-1019, 1988.
- 11) Lukse MP, Vacc NA: Grief, depression, and coping in women undergoing infertility treatment. *Obstet Gynecol* 93: 245-251, 1999.
- 12) Yong P, Martin C, Thong J: A comparison of psychological functioning in women at different stages of *in vitro* fertilization treatment using the mean affect adjective check list. *J Assist Reprod Genet* 17: 553-556, 2000.
- 13) Golombok S: Psychological functioning in infertility patients. *Hum Reprod* 7: 208-212, 1992.
- 14) Black RB, Walther VN, Chute D, Greenfield DA: When *in vitro* fertilization fails: a prospective view. *Soc Work Health Care* 17: 1-19, 1992.
- 15) Bergart AM: The experience of women in unsuccessful infertility treatment: what do patients need when medical intervention fails? *Soc Work Health Care* 30: 45-69, 2000.
- 16) Demyttenaere K, Bonte L, Gheldof M, Vervaeke M, Meuleman C, Vanderschuerem D, D'Hooghe T: Coping style and depression level influence outcome in *in vitro* fertilization. *Fertil Steril* 69: 1026-1033,

- 1998.
- 17) Smeenk JMJ, Verhaak CM, Eugster A, van Minnen A, Zielhuis GA, Braat DDM: The effect of anxiety and depression on the outcome of *in-vitro* fertilization. *Hum Reprod* 16: 1420-1423, 2001.
  - 18) Fanchin R, Gellman S, Righini C, Ayoubi JM, Olivennes F, Frydman R: Uterine contraction frequency at the time of embryo transfer (ET) is correlated with anxiety levels [abstract no. P499]. In: Program and abstracts of the 56<sup>th</sup> Annual Meeting of the American Society for Reproductive Medicine. San Diego, CA: *Fertil Steril* 74: S252, 2000.
  - 19) Harrison RF, O'Moore RR, O'Moore AM: Stress and fertility: some modalities of investigation and treatment in couples with unexplained infertility in Dublin. *Int J Fertil* 31: 153-159, 1986.
  - 20) Edelmann RJ, Golombok S: Stress and reproductive failure. *J Reprod Infant Psychol* 7: 79-86, 1989.
  - 21) Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR: The effect of specific emotional stressor on prolactin, cortisol and testosterone concentrations in women varies with their trait anxiety. *Fertil Steril* 52: 942-948, 1989.
  - 22) Merari D, Feldberg D, Elizur A, Goldman J, Modan B: Psychological and hormonal changes in the course of *in vitro* fertilization. *J Assist Repro Genet* 9: 161-169, 1992.
  - 23) Matsubayashi H, Hosaka T, Izumi S, Suzuki T, Makino T: Emotional distress of infertile women in Japan. *Hum Reprod* 16: 966-969, 2001.
  - 24) Sanders KA, Bruce NW: A prospective study of psychosocial stress and fertility in women. *Hum Reprod* 12: 2324-2329, 1997.
  - 25) Domar AD, Zuttermeister PC, Seibel MM, Benson H: Psychological improvement in infertile women after behavioral treatment: a replication. *Fertil Steril* 58: 144-147, 1992.
  - 26) Sarrel PM, DeCherney AH: Psychotherapeutic intervention for treatment of couples with secondary infertility. *Fertil Steril* 43: 897-900, 1985.
  - 27) Domar AD, Clapp D, Slawby EA, Dusek J, Kessel B, Freizinger M: Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil Steril* 73: 805-812, 2000.

### Appendix I

Questionnaire used in our study with visual analog scales. We asked the patient to retrospectively describe her feelings before, during and after infertility treatments, two months prior to conception and surrounding conception. Questions were given in this order.

1 If you set most delighted experience at + 100 and most sorrowful experience at - 100, express your feeling between - 100 and 100 at each time point.



2 If you set most anxious experience at + 100 and most relieved experience at - 100, express your feeling between - 100 and 100 at each time point.

3 If you set most pressured experience with being infertile at + 100 and least pressured experience at - 100, express your feeling between - 100 and 100 at each time point.

4 If you set most manic experience at + 100 and most depressed experience at - 100, express your feeling between - 100 and 100 at each time point.

5 If you set most relaxed experience at + 100 and most tense experience at - 100, express your feeling between - 100 and 100 at each time point.

6 If you set strongest experience to hope for having children at + 100 and weakest experience at - 100, express your feeling between - 100 and 100 at each time point.

7 If you set having best understanding/support from your husband at + 100 and having worst understanding/support at - 100, express your feeling between - 100 and 100 at each time point.

8 If you set most vigorous experience at + 100 and least vigorous experience at - 100, express your feeling between - 100 and 100 at each time point.



- 9 If you set most irritable experience at + 100 and least irritable experience at - 100, express your feeling between - 100 and 100 at each time point.
- 10 If you set most fatiguing experience at + 100 and least fatiguing experience at - 100, express your feeling between - 100 and 100.