Epidemiology of Infertility and Recurrent Pregnancy Loss in Society with Fewer Children

JMAJ 52(1): 23–28, 2009

Harumi KUBO*1

Abstract

Since there has been no improvement in the current downward trend in Japan's birth rate, the growing population of potential patients with infertility is a significant social problem. Underlying the factors of infertility are psychological factors related to the current stress of modern-day society, sexually transmitted diseases, increased smoking rates among young females, weight abnormalities such as obesity and underweight resulting from diet, an age-related decrease in reproductive function resulting from late marriage and late childbearing (social infertility), and increasing numbers of patients with polycystic ovary syndrome, endometriosis, or uterine myoma. Eighty to 90% of these factors contributing to infertility are derived from personal lifestyle and are considered to be preventable. On the other hand, 50–70% of recurrent pregnancy loss is of unknown cause, and currently there are no established standard tests or treatment policies. However, it is important to carry out close systematic investigation of the couple to determine the cause of infertility, including chromosomal or endocrine factors, blood coagulation function, uterine deformity, autoimmune diseases, and infectious diseases. Treatment specific to the cause should be provided to the patient, and the cause should be prevented if possible. It is proposed that, to prevent infertility and recurrent pregnancy loss, males and females of reproductive age undergo regular check-ups of reproductive function once a year. It is expected that this kind of effort may lead to improvement of the downward trend in the birthrate.

Key words Infertility and recurrent pregnancy loss, Declining birth rate, Assisted reproductive technology, Infertility prevention activities

Infertility/Recurrent Pregnancy Loss and Declining Birth Rate

Infertility is decreased or complete lack of fecundity due to impaired reproductive function, which is essential for the continuation of life. Fecundity is the ability to establish a clinical pregnancy in the cycles of a couples' reproductive activities. In contrast, in cases of recurrent pregnancy loss, fecundity is maintained, but fails to produce newborns. Recurrent pregnancy loss includes recurrent abortion (2 or more miscarriages) and habitual abortion (3 or more miscarriages).

Although various fecundity curves in relation to the age of females have been reported, the probability of establishing pregnancy per reproductive cycle among sexually mature couples who wish to have a child is considered to be 20–25%. Of couples who want to have a child, 80% and 90% achieve pregnancy within a year and within 2 years, respectively. In Japan, infertility refers to the absence of pregnancy after at least 2 years of normal sexual activity by a couple that wants to achieve pregnancy. However, in western countries, infertility is defined as a couple's inability to conceive after one year of regular sexual intercourse. Considering the recent trends of late marriage, late childbearing, and falling birthrates in Japan, the definition of the inability to conceive after one year of sexual life seems to be more appropriate.

*1 Chief Director, NPO Japan Reproductive Health Association, Tokyo, Japan (profhkubojp@yahoo.co.jp).
This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol.137, No.1, 2008, pages 17–22).

Infertility is regarded as a medical problem if medical intervention is required to achieve conception when an infertile couple wants to have a child.

The population of individuals with potential infertility is said to be 10–15% of the overall population of reproductive age, yielding an estimated 2,400,000 infertile individuals in Japan. According to the American Society for Reproductive Medicine (ASRM), there are 6,100,000 infertile individuals in the US. A World Health Organization (WHO) survey of 7,273 couples with infertility revealed that infertility was attributable to female factors alone in 41% cases, both male and female factors in 24%, male factors alone in 24%, and unknown causes in 11%.

Despite the fact that infertility is common in both men and women, it differs from life-threatening diseases including cancer or AIDS, so no one worries about the possibility that he or she may be infertile or makes an effort to prevent infertility. The reason for this may be that, even if the individual is infertile, various organs of the cardiovascular system, alimentary system, etc., which are important for the health and life sustaining of the individual are normal and cause no problems in daily living activities. Therefore, individual patients generally do not recognize abnormalities of the reproductive system until they marry and attempt to conceive a child.

However, in Japan late marriage and late childbearing have become increasingly common, and thus more women tend to have the first child in their early to late 30s, resulting in a situation in which most women recognize their infertility and recurrent pregnancy loss in their late 30s. Along with aging, ovarian reserve decreases and abnormalities of the genital organs increase, making infertility more intractable. Therefore, considering the current social situation of Japan, women younger than 35 years who have failed to conceive after one year of trying and those aged 35 years or older who have failed to conceive after 6 months of trying are likely to be infertile and should undergo examination for infertility early, regardless of the current definition of infertility.

In general, a healthy child can be expected at delivery if a pregnancy has been established, but unfortunately the rate of miscarriage is 34% for women in their 40s and 18% for those in their 30s. In contrast, the corresponding rate is about 10% for women in their 20s.[1] Thus, the probability of having a healthy newborn is related to the maternal age, a phenomenon reportedly associated with maternal age-related chromosomal abnormality (aneuploid) of the fertilized egg.

On the other hand, recurrent pregnancy loss, sometimes included in broadly defined infertility, generally refers to the failure of having a child because of recurrent abortion or stillbirth after the establishment of pregnancy. This term is considered to be synonymous with habitual abortion. Therefore, balanced chromosomal translocation, autoimmune disease, and uterine malformation of the parent, rather than accidental chromosomal abnormality of the fertilized egg, are known to be causes. However, the cause of recurrent pregnancy loss is unknown in most cases, and thus has no strict medical definition. Recurrent pregnancy loss is currently a syndrome covering a wide spectrum of clinical conditions including repeated intrauterine fetal death in or after the second trimester.

Actual Status of Medical Care for Infertility and Recurrent Pregnancy Loss

Assisted reproductive technology (ART) has become much more common in Japan as well as in other countries since the world's first baby conceived through in vitro fertilization was born in the UK in 1978. ART is now commonly available in university hospitals and infertility clinics, serving as a useful treatment for infertility in this society with its decreasing numbers of children and providing good steady results. Childbirth by ART as a whole—including in vitro fertilization and embryo transfer (IVF-ET)—has been increasing year by year, and the number of ART-related births is over 19,000 per year, and over 150,000 cumulatively (as of 2005).[2] In addition, in regard to male infertility factors such as severe azoospermia and asthenozoospermia, medical procedures for intractable male infertility have been common since the development of the technique of intracytoplasmic sperm injection (ICSI).

On the other hand, high frequencies of balanced chromosomal translocation among patients with recurrent pregnancy loss have long been reported. In translocation, chromosomes break at two sites and switch positions when rearranged. Since total gene dosage remains unchanged, with all the necessary gene dosage being present, the carrier of a balanced translocation is normal and

has no difference in health from those without translocation. However, when gametes (egg and sperm) are formed, it is possible that the egg or sperm may have an imbalance in the distribution of genetic material, and the egg or sperm with the translocational imbalance may abort spontaneously even if fertilized.

In this connection, preimplantation genetic diagnosis (PGD) of patients with recurrent pregnancy loss is attracting attention these days. Through this technique, one or two blastomeres from each four- to eight-cell stage embryo obtained through ART are submitted to karyotypic analysis of chromosomes, and only the embryo with normal or a balanced translocation is used for transfer to prevent abortion. In Japan, the use of PGD was discussed carefully because of the concern that PGD of genetic disorders may be related to the concept of eugenics, and the Japan Society of Obstetrics and Gynecology has drawn up a societal rule that PGD only be permitted on a case-by-case basis under an approval system limited to serious genetic disorders. However, since 2006, PGD of fertilized eggs using ART has begun to be reviewed and permitted for individual cases to prevent recurrent pregnancy loss. However, PGD of fertilized eggs still has many problems including the presupposition that ART be applied to females who are capable of achieving a natural pregnancy, and the lack of difference between birth rates in cases of followed natural pregnancy and those in cases of PGD.[3]

There are also issues of financial and psychological burden on couples with infertility or recurrent pregnancy loss, because ART is not covered by health insurance. In actuality, there are considerable differences in expenses borne by patients among different institutions. Considering the context of these circumstances around reproductive medicine and the future means of practicing infertility treatment in a society characterized by a declining birth rate, it would appear meaningful to provide insurance coverage of care for infertility and recurrent pregnancy loss.

Epidemiology and Prevention of Infertility and Recurrent Pregnancy Loss

In Japan, where there has been no reversal in the declining birth rate, the tendency toward increasing potential infertility factors is a major social issue. Such factors include psychological factors caused by the stresses of modern society, sexually transmitted diseases, increased smoking rates among young women, weight abnormalities such as obesity and underweight, decreased reproductive function resulting from late marriage and late childbearing (social infertility), and gynecologic disorders such as polycystic ovary syndrome, endometriosis, and uterine myoma. Of these infertility factors, 80–90% are related to the individual's lifestyle and thus considered to be preventable (Table 1).

Table 1 Preventable infertility factors

• Lifestyle
Irregular lifestyle habits
Life environment, stress
Smoking, drinking
Obesity, underweight, diet
Pregnancy in adolescence, induced abortion
Favorite foods, regularly used drugs
Occupational diseases, environmental endocrine disrupters
• Lifestyle-related diseases
Metabolic syndrome
ED (erectile dysfunction), FSD (female sexual dysfunction)
• Endocrine and debilitating diseases
Polycystic ovary syndrome (insulin-resistant)
Endometriosis
Menstruation-related syndrome
Hypothalamic-pituitary-ovarian dysfunction
Autoimmune disease
Anemia
• Infectious diseases
STD (Chlamydia trachomatis, Neisseria gonorrhoea, etc.)
Pelvic infectious disease
Tuberculosis
Viral disease, febrile disease
• Iatrogenic infertility
Pelvic surgery
Radiotherapy and chemotherapy for malignant tumor
Asherman's syndrome
Tubal interruption and vasoligation
Conization
• Social infertility
Aging, late marriage, late childbearing
No marriage, no childbearing
Sexless couples
Homosexuals

On the other hand, the cause remains unclear in 50–70% of cases of recurrent pregnancy loss, and there is no established standard examination or any treatment policies. However, it is important to carry out systematic testing of chromosomes, endocrine factors, blood coagulation function, uterine deformity, autoimmune diseases, and infec-

tions in parents to elucidate the cause. Patients should receive treatment specific to the cause, and the cause, if preventable, should be eliminated. The etiology and epidemiology of infertility and preventive measures are described in the following paragraphs.

Psychologic stress

Psychologic stress is defined as the perception of a threat or obstacle. In the early phase of stress, bodily systems increase their activities. This increase in activities is further enhanced by the excessive secretion of adrenaline from the adrenal gland and sympathetic nervous system. Therefore, acute stress is manifested as increased heart rate, elevated blood pressure, increased respiratory rate, perspiration, and cold sensation. However, conversely, chronic stress induces depression and suppressed immune function.

Couples undergoing treatment for infertility or recurrent pregnancy loss are under enormous chronic stress. However, there are almost no reports documenting the responsibility of stress itself for inducing infertility or recurrent pregnancy loss. However, it has been reported that high stress may cause impaired hormone production, suppressed ovulation, spasmus of the uterine tube, or defect in spermatogenesis resulting from pelvic circulatory disturbance.

It is also said that endometriosis, which is related to infertility, has been increasing recently. According to 1997 data from the then Ministry of Health and Welfare, about 120,000 women visited healthcare facilities because of endometriosis, and the number of patients as a whole was estimated to be about 1,000,000. In particular, endometriosis is more common in women in their early 30s, with a reported prevalence rate of one per 150, although the actual prevalence is thought to be slightly higher. The cited causes of endometriosis include a complex social life and other stress factors. Disrupted hormone balance due to these factors causes the suppression of ovarian function. For instance, it is generally considered that endometriosis is aggravated by stress related to daily or social rhythms including irregular eating and sleeping, busyness, or boredom and interpersonal relationships. In addition, the content of dioxin, an endocrine-disrupting chemical, in breast milk in Japan is reportedly 10- to 200-fold higher than the European standard. It is speculated that various chemicals also contribute to the occurrence of endometriosis.

There are various measures to prevent stress, depending on the social environment of the individual. However, in general, it is useful to abstain from stimulants such as caffeine, and to be open and emotionally available. Other methods include exercise, yoga, and other hobbies to reduce stress, consulting a psychologist or counselor to keep peace of mind, and practicing religious devotion.

Habitual smoking

Although not widely known, habitual smoking carries the risk of jeopardizing reproductive function as well as inducing respiratory or circulatory disorders and cancers. Although smoking has generally been decreasing in both men and women in Japan in recent years, there is concern that the percentage of smokers has been increasing among young women who have not yet reached sexual maturity, with the smoking rate currently about 25% (1 out of 4 persons).

It is apparent from the results of studies that smoking is injurious to ovarian function, and the degree of damage is thought to depend on the amount and duration of smoking. Nicotine, tar, and other chemical substances contained in tobacco suppress the production of estrogen and other ovarian hormones related to ovulation, and induce gene defects of the egg. This may accelerate follicle atresia and result in early menopause. The risk of early menopause occurring at the age of 44 years or younger is about 2-fold higher in women who smoke than in those who do not. It has also been reported that not only smoking but also secondhand smoking accelerates menopause by about 2 years. When age is matched, the prevalence of menopause is 10–20% higher in females with smoking or secondhand smoking. Damage from smoking may not be partly reversible, but it is possible to halt further increases in damage as a result of smoking cessation. Young women who smoke may think that smoking is trendy, looks nice, or will make them more slender, and they may ruin their health as a result of smoking. Although the responsibility for such damage rests with the smokers themselves, warnings should be given.

Among males, when benzopyrene (an ingredient found in tobacco)-bound sperm DNA is detected by staining, the score calculated from the detection rate and concentration is significantly higher in smokers. The score has been

correlated with the concentration of cotinine (a metabolite of nicotine in the body) in semen. In smokers, the majority of sperm are benzopyrene-bound, and these factors are considered to cause fragmentation of sperm DNA, creating a factor for infertility.

Weight factors

It has been pointed out that obesity or underweight is involved in about 12% of female cases of infertility. Infertility risk is 2.7-fold higher in obese women (body mass index [BMI]>30). A similar trend is also observed in thin women. It has been reported that obese women have lower rates of egg collection and conception after any infertility treatment including ART, and exhibit higher rates of initial miscarriage.

The correlation between body weight and fertility is mainly based on the fact that the excessive estrogen produced in fat cells suppresses the production of ovarian steroids. In obese women, excessive estrogen causes a decrease in the possibility of conception, almost as if it were a contraceptive. Conversely, in thin women, estrogen production in fat cells is insufficient, causing irregular menstrual cycles and possibly inducing early menopause. In any case, inadequate weight can lead to impaired ovulation and irregular sexual menstrual cycles.

In men, obesity causes an increase in aromatase activity in fat cells, inducing hyperestrogenism and suppression of the hypothalamic-pituitary-testicular system. This also causes hypoandrogenism, resulting in suppressed spermatogenesis and sexual function.

Sexually transmitted diseases (STDs)

Everyone recognizes the possibility of conception when unprotected intercourse occurs. However, it is not well known that the risk of contracting an STD is increased if condoms are not used. Contracting an STD is likely to damage future fertility. STDs can be transmitted by unprotected sexual contact, and epidemiologists consider that one in three sexually active young people may contract an STD by the age of 24 years. Common STDs include chlamydia infection, gonorrhea, syphilis, genital herpes, scabies, crab lice, and HIV. Since these STD infections have few characteristic symptoms, it is possible that patients are unaware of their STD infection, and thus the disease may become intractable and cause sequelae (e.g., infertility) as well as causing secondary infections in sexual partners.

Chlamydia infection, the main cause of salpingitis and pelvic peritonitis, can induce infertility. Chlamydia DNA is detected from the cervical mucus in an average 29% (25–50%) of patients with the above diseases.[4] In recent years, STD infections have also been increasing in Japan; STD surveillance has found chlamydia infection in 2–3% of subjects, and gonorrhea in 0.5–1.5%. However, this chlamydia infection rate is based only on hospital visitors. In a survey covering 3,190 randomly selected high school students (by the Japanese Society for Sexually Transmitted Diseases in 2004), the overall chlamydia infection rate was 11.4% (7.3% for males and 13.9% for females), with the highest rates by age being 8.6% and 23.5% for males and females, respectively, at the age of 16 years.[5]

To prevent infertility, including cases from STDs, it is useful to carry out annual screenings for reproductive function in males and females who have reached reproductive age. To achieve the most accurate chlamydia examination, urine, cervical mucus, or urethral mucus samples should be used to detect antigens of Chlamydia trachomatis by the PCR or LCR technique. However, in view of the necessary time and cost, it is useful to measure the serum antibody titer for a screening test.

Aging (social infertility)

Social infertility cases related to late marriage and late childbearing recently have been increasing in Japan. About 20% of couples do not intend to have their first child until at least age 35. However, it is biologically evident that reproductive capacity decreases with age, and that decreased chance of pregnancy is a physiologic change that occurs with aging. However, hardly any women are aware of the fact that the age-related decrease in reproductive capacity begins in the late 20s.

Females have more than a million oocytes at the time of birth. These oocytes gradually become atretic follicles, and the number of oocytes decreases to about 300,000 in puberty. During the subsequent life of the woman, no eggs will be regenerated. Therefore, the number of eggs in a woman decreases steadily with aging. In addition, aged eggs are associated with higher frequencies of chromosomal abnormality (aneuploid), and as a result, the infertility rate and

miscarriage rate increase with aging. Although the infertility rate remains less than 10% in women under 30 years of age, problems in fertility occur in 15% of them in their early 30s and in about 22% of them in their late 30s. It is thought that after 40 years of age, about 30% of women have no chance of natural pregnancy.[6]

However, the rate of aging in reproductive function varies among different individuals. It is therefore difficult to set criteria for evaluating the annual changes in fertility of each woman. It recently has become possible to estimate age-related ovarian reserve by determining the levels of FSH, basal E2, anti-Mullerian duct hormone (AMH), and inhibin B on day 3 of the menstrual cycle. If the ovarian reserve shows accelerated aging as compared with the physical age, fertility is considered to be decreased, encouraging early childbearing and suggesting a poor prognosis for infertility treatment. Social infertility due to aging is a by-product of the modern gender-equal society. It is important to consider the couple's situation in light of their work-life balance.

On the other hand, in men, the testes begin to shrink and soften in the 40s, resulting in slightly deteriorated spermatogenesis, decreased motility of sperm, and increased numbers of sperm with morphological or chromosomal abnormalities. However, weakening of the reproductive and sexual functions in men is not as rapid a change as is menopause in women. If physically healthy, men may have testes that maintain spermatogenesis even into their 90s.

References

1. Whitman-Elia GF, Baxley EG. A primary care approach to the infertile couple. J Am Board Fam Pract. 2001;14:33–45.
2. 2006 Report of the Ethics Committee and the Registry and Survey Subcommittee of the Japan Society of Obstetrics and Gynecology. Journal of the Japan Society of Obstetrics and Gynecology. 2007;59:1717–1739. (in Japanese)
3. Sugiura-Ogasawara M, Ozaki Y, Sato T, et al. Poor prognosis of recurrent aborters with either maternal or paternal reciprocal translations. Fertil Steril. 2004;81:367–373.
4. Hull MG, Glazener CM, Kelly NJ, et al. Population study of causes, treatment, and outcome of infertility. Br Med J (Clin Res Ed). 1985;291:1693–1697.
5. Imai H. A large-scale screening survey on asymptomatic chlamydia infection in high-school students: Urgent progress report issued because of high infection rates (conference minutes). Japanese Journal of Sexually Transmitted Diseases. 2004;15:55. (in Japanese)
6. Menken J, Trussell J, Larsen U. Age and infertility. Science. 1986;233:1389–1394.