Vol.47, No.4 April 2004

JMAJ

Japan Medical Association Journal

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Elucidation of the Mechanism of Antibiotic Resistance Acquisition of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and Determination of Its Whole Genome Nucleotide Sequence

JMAJ 47(4): 153–159, 2004

Keiichi HIRAMATSU

Professor, Department of Microbiology and Infection Control Science, Faculty of Medicine, Juntendo University

Abstract: Although *Staphylococcus aureus* is a member of normal human flora, it may cause fatal infection to humans who underwent accidental injury or surgical operation. The bacteria is potent in acquiring antibiotic resistance, and is now a very important causative agent of hospital acquired infection. The most important mechanism of the antibiotic resistance acquisition is via staphylococcal cassette chromosome (SCC), a mobile DNA specific to staphylococci, which has had attained molecular evolution for the interspecies exchange of genetic information. Methicillin-resistant *S. aureus* (MRSA) has been born by acquiring penicillin/cephalosporin resistance that was carried by an SCC. Moreover, hospital MRSA has become multiply resistant to antibiotics, and finally acquired resistance to the "last resort" antibiotic vancomycin.

Key words: *Staphylococcus aureus*; Methicillin resistance; Vancomycin resistance; SCC*mec*; Genome

Introduction

Successful purification of penicillin G in 1941 marked the advent of the history of modern anti-microbial chemotherapy. However, it took only a few years before strains of *Staphylococcus aureus* producing penicillin-hydrolyzing enzyme (penicillinase) started to prevail. In the latter half of the 1950s, *S. aureus* multiply resistant to all the available antibiotics developed by that time (such as erythoromycin, streptomycin etc.) prevailed the hospitals all over the world. In medical journals of those days we find articles reporting the critical situation of hospital infection which is very much similar to the recent situation of ours.

Development of a semi-synthetic penicillin, methicillin, which resists the hydrolysis by peni-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 129, No. 1, 2003, pages 53–59).
This research was awarded the Medical Prize of the Japan Medical Association for 2002 in Basic Medicine.

cillinase, together with subsequent launch of the first generation cephalosporins, have exerted a great power to expel these troublesome multi-resistant bacteria from the hospitals in the 1960s. However, as early as in 1960, the year of methicillin development, Jevons noticed an *S. aureus* strain that can grow in the presence of methicillin.[1] In the following year she reported her observation that was the first isolation of methicillin-resistant *S. aureus* (MRSA).

MRSA did not cause much trouble to draw attention of clinicians in the following decade. However, it started to cause nosocomial infection frequently in Europe and US hospitals, followed by a steep rise of incidence of MRSA in Japanese hospitals in the early 1980s.

S. aureus is a part of normal human flora. The aim of my research was directed to understand how such a familiar bacterium turned out to be a treacherous human pathogen resisting all the fruits of modern antimicrobinal chemotherapy.

How did *S. aureus* Acquire Methicillin Resistance?

1. *mecA* gene

MRSA resists not only to methicillin but to all available beta-lactam antibiotics including penicillin and cephalosporin derivatives. The mechanism of resistance of MRSA has not been uncovered until the mid-1980s. Beta-lactam antibiotics kill bacteria by inhibiting the cell-wall synthesis. In the early 1980s, such researchers as P. Reynolds, T. Yokota, and A. Tomasz reported that some MRSA strains produce a strange penicillin-binding protein (PBP) besides the intrinsic sets of *S. aureus* PBPs. The PBP, now denoted PBP2′ or PBPa, seemed to have reduced binding affinity to beta-lactam antibiotics. Derivation of PBP2′ remained to be solved. In 1986, M. Matsuhashi cloned the gene *mecA* encoding the PBP2′, and has shown that the gene is not found in methicillin-susceptible *S. aureus* strains.[2] The next question was whether *mecA* is transmissible across *S. aureus* strains or not.

2. Staphylococcal cassette chromosome *mec* (SCC*mec*)

In 1995, by cloning of the chromosomal DNAs around *mecA* gene, we showed that *mecA* gene is carried by a big DNA fragment (*mec* region DNA) that corresponds to about 1–2% of the entire *S. aureus* chromosome, and that there are at least three distinct types in the *mec* region DNA that are found in the MRSA clinical isolates in the world. In 1999, we determined the nucleotide sequence of one of the *mec* region DNA,[3] and have shown that the *mec* region DNA is a novel mobile DNA that is capable of site-specific integration into and precise excision from *S. aureus* chromosome.[4] We designated the *mec* region DNA as staphylococcal cassette chromosome *mec* (SCC*mec*), and the two novel genes responsible for the movement of the element as cassette chromosome recombinase A and B (*ccrA* and *ccrB*).[4]

We subsequently showed that there are three allotypes in the *ccrA,B* genes and more than four classes in the "*mec* gene complex" (which is composed of *mecA*, and its regulator genes *mecI* and *mecR1* located next to it), and that the SCC*mec* elements carried by the MRSA strains in the world are divided into three types defined by the combination of the type of *ccr* genes and class of *mec* gene complex.[5]

Step-Wise Expression of Methicillin Resistance by *S. aureus*

1. pre-MRSA

S. aureus does not express methicillin resistance even if it has acquired SCC*mec*. A strain that has acquired *mecA* gene together with its regulator genes, *mecI* and *mecR1*, remains susceptible to methicillin. We identified such clinical strain and designated it pre-MRSA, and proposed the idea that mutational inactivation of *mecI* gene (that encodes potent repressor of *mecA* gene transcription) is necessary for pre-MRSA to become MRSA.

2. hetero-MRSA

When *mecI*-mediated repression is released by mutation, "hetero-MRSA" emerges. This class of MRSA still remains susceptible to higher concentrations of methicillin (and low concentrations of potent beta-lactam antibiotics such as imipenem). This is explained by the hypothesis that the physiological status of the *S. aureus* cell is not appropriate to take a full advantage of the function of the exogenous cell-wall synthesis enzyme PBP2′. Hetero-MRSA is named as such since the cells of various degrees of methicillin-resistance spontaneously emerge within its cell population.

3. homo-MRSA

With high frequencies of one in $10^{-4–5}$ mutant strains emerge from hetero-MRSA whose cell population is composed of the cells with "homogeneously high" methicillin-resistance. Many researchers including B. Berger-Bachi and A. Tomasz groups have been working for the mechanism how this mutational conversion occurs. We have also cloned two genes, *hmrA* and *hmrB*, whose overexpression raise methicillin resistance of a hetero-MRSA strain to the level of homo-MRSA. However, we still do not know how they function in raising methicillin resistance.

Vancomycin Resistance of MRSA

Besides beta-lactam, MRSA is resistant to practically all antibiotics belonging to other classes of anti-microbial function. Vancomycin had been considered as the last resort antibiotic before 1996 when we identified the first vancomycin-resistant MRSA strain from a 4-months-old baby whose surgical wound infection did not respond to vancomycin therapy.[6] Strain Mu50, which we designated vancomycin-resistant *S. aureus* (VRSA), recorded vancomycin MIC of 8 mg/*l*. (The strains of MIC 8 and 16 mg/*l* are called vancomycin-intermediate *S. aureus* [VISA] by some researchers, but it should be pointed out that the infection with MRSA strains with MIC 4 and above are difficult to treat by vancomycin therapy, thus are clinically "resistant".)

1. Low-level vancomycin-resistant *S. aureus* (L-VRSA)

Now that highly vancomycin-resistant *S. aureus* with a different mechanism has been reported in US in 2002, we call Mu50 and other strains in the world with MIC levels of 8 and 16 mg/*l* low-level vancomycin-resistant *S. aureus* (L-VRSA). After our report of Mu50, L-VRSA strains have been isolated from all over the world including US, England, France, Greece, Brazil, Korea, South Africa, and Taiwan, indicating that the resistance acquisition is a global issue.

2. hetero-L-VRSA

Our discovery of L-VRSA was preceded by that of hetero-L-VRSA (or hetero-VRSA) in 1996.[7] We isolated MRSA strain Mu3 from a 65-year-old patient whose MRSA pneumonia resisted vancomycin therapy. Mu3 recorded susceptible level of vancomycin MIC (2 mg*l*). However, using a more sensitive susceptibility test called "population analysis", we recognized that the Mu3 strain contains the cells with various levels of vancomycin resistance (capable of growth in the presence of 4–8 and 9 mg/*l* of vancomycin). We named the strain, hetero-VRSA (now better be called hetero-L-VRSA due to the reason described above) in analogy with the hetero-resistance in methicillin resistance. Mu50 happened to have the same pulse-field gel electrophoresis (PFGE) pattern with that of Mu3, indicating that Mu50 was closely related to Mu3.

3. Conversion from hetero-L-VRSA to L-VRSA

The conversion from hetero-L-VRSA to L-VRSA is due to spontaneous mutation (Kapi, M. in preparation). By analyzing 16 L-VRSA strains isolated from 7 countries, we noticed that the cell-wall of the L-VRSA strains was sig-

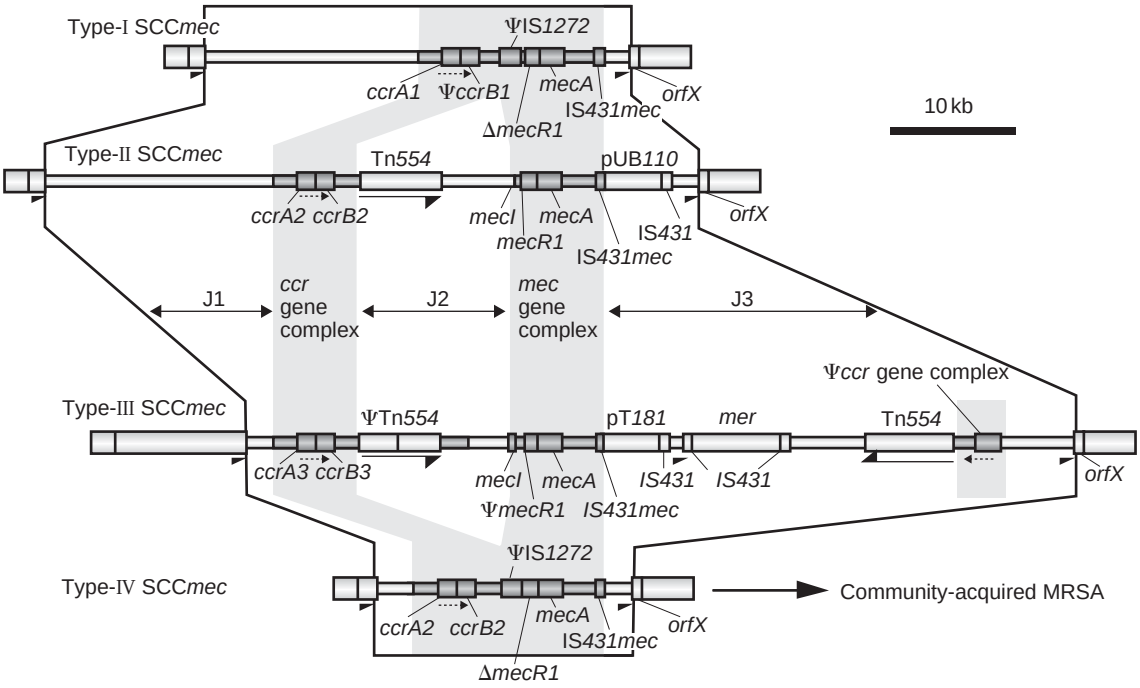

Fig. 1 Four types of SCC*mec* found in MRSA

Types I–III are those found in MRSA strains prevailing in the hospitals of the world. They have big J regions (J stands for junkyard). J region contains several pseudogenes seemingly useless for the host cells. It also serves as the depot for resistance genes against non-beta-lactam antibiotics such as macrolide (encoded by Tn*554*), mercury (*mer*) and tetracycline (pT181). Type IV is a small SCC*mec* widely found in the MRSA strains prevailing in the community.

nificantly thicker than those of control strains. By utilizing a defined cell-wall synthesis media, we demonstrated the importance of increased number of peptidoglycan layers in the cell wall to prevent the penetration of vancomycin molecules to the cytoplasmic membrane where the targets of vancomycin are present. Based on these data, we proposed an affinity trapping model for vancomycin resistance.[8)]

Evolution of MRSA into the New Direction

As a hospital pathogen, MRSA continues to evolve into multiple resistance; the culmination of it being the acquisition of vancomycin resistance. There is always an environmental pressure before the bacteria evolves itself. Diverse classes of antibiotics used in the hospital obviously constitute the selective pressure exerted on the nosocomial pathogens.

On the other hand, in the past several years, some researchers became aware of a novel trends in MRSA epidemiology. Center of Disease Control and Prevention (CDC) reported the death of four children in the two US states in 1999. The children independently contracted severe pneumonia caused by MRSA whose antibiogram patterns were different from those of hospital MRSA strains. We identified a new SCC*mec* (type IV) in such community-acquired MRSA (C-MRSA) strains, and thus proved that distinct MRSA strains have been prevailing outside the hospital.[5)]

As shown in Fig. 1, the type-IV SCC*mec* is much smaller in size than the other three types of SCC*mec* found in the hospital, and has few genes other than those with the cardinal function, *ccr* genes and *mec* gene complex.

The phenotypic characteristics of C-MRSA strains are rapid growth rate, susceptibility to multiple antibiotics other than beta-lactam,

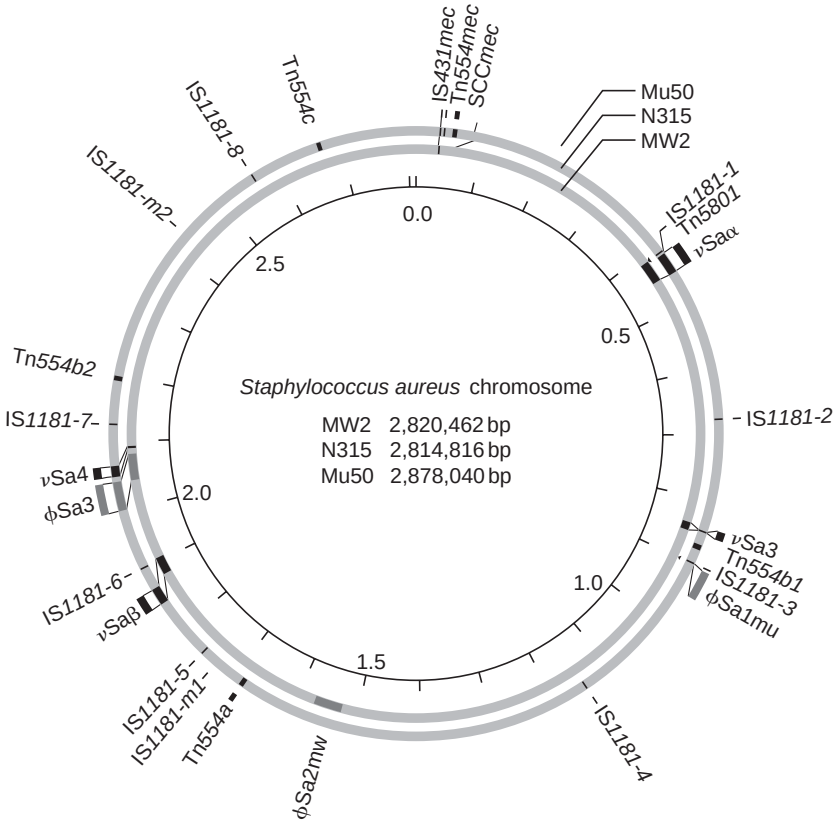

Fig. 2 Comparison of the chromosomes of three MRSA strains. (from reference 10)
All are circular DNAs of about 2.8 Mbp in size. More than 90% of the sequence are conserved among the three. Medically important feature of individual *S. aureus* strain such as pathogenicity and antibiotic resistance is determined by the sum of the allotype of genomic islands (Gislands). The names of the Gislands and their encoded function in paretheses, in clockwise rotation, are: SCC*mec* (methicillin and other drug resistance), νSaα (superantigen), νSa3 (enterotoxins), ϕSa1mu (unknown), ϕSa2mw (Panton-Valentine leukocidins), ϕSa3 (enterotoxins), νSaβ (enterotoxins, bacteriocin), νSa4 (unknown). IS, insertion sequence; Tn (transposon).

and high virulence reported with some strains. As described below, we could correlate these features of C-MRSA to its genome structure in comparison with that of hospital-acquired MRSA (H-MRSA).

The Feature of *S. aureus* as Inscribed in Its Genome

To explore how multi-antibiotic resistance is acquired by H-MRSA strains and how the high virulence of strain is expressed by a certain C-MRSA strains, we have determined whole genome sequence of L-VRSA strain Mu50, pre-MRSA strain N315, and MW2, a C-MRSA strain isolated from one of the four victims of paediatric deaths.[9,10] This turned out to be the first determination of the entire genome sequence of *S. aureus*. The feature of *S. aureus* genome is as follows (Fig. 2).

About 2,600 genes are found on the chromosome of about 2.8 Mbp in size, 52% of which have the highest homology to the orthologues of *Bacillus subtilis* or *Bacillus halodurans*, the species that has no virulence to humans. Those genes are mostly house-keeping genes involved in such metabolic processes as synthesis of nucleic acids and proteins. This implies that

S. aureus and *Bacillus* species share a common ancestor in the early days of species diversification. The feature of *S. aureus* as a human pathogen is determined by another functional domain of the chromosome. *S. aureus* chromosome contains several genomic islands (Gislands) that are found at least at seven different loci thus interrupting the domain of chromosome encoding house-keeping function which descended from the ancestor.[10] In these Gislands, most of the genes involved in pathogenesis and antibiotic resistance are identified.

1. Gislands

SCC is one of the Gislands. Besides the SCC*mec* carrying most of the chromosomally localized antibiotic resistance genes, SCC can carry such genes involved in capsule formation that constitutes a part of virulence potential of the organism. Prophages as a subfamily of Gisland are integrated at specific chromosomal loci encode virulence genes. In MW2, one of the prophages carries Panton-Valentine leukocidin genes that encode potent cytotoxin against human white blood cells.[10] Thus, Gislands are the regions of the chromosome that have been laterally (in contrast to vertical transmission) acquired from other bacterial species or strains. Gislands are discriminated from the surrounding chromosome by their subtle difference in the nucleotide composition (GC contents etc.) or the codon usage preference. Further identification of Gislands by comparison with other staphylococcal species and close examination of the gene function carried by the Gislands will reveal the history how *S. aureus* has evolved itself as a human pathogen.

2. Gisland allotyping

Comparison of the chromosome of C-MRSA strain MW2 with those of H-MRSA strains N315 and Mu50 reveals striking difference in the genes present in Gislands. For example, on the νSaα island, we find a cluster of genes encoding superantigens. While N315 and Mu50 had almost identical repertoire of the superantigen genes (though, one of the 10 genes in N315 was missing in Mu50). However, none of the peptides encoded by 11 genes of MW2 was identical with those of N315/Mu50. In another island νSaβ of N315 and Mu50, a cluster of enterotoxin genes (responsible for food poisoning) are present. The corresponding island of MW2, however, does not contain enterotoxin genes. Instead a novel operon involved in the production of bacteriocin (the toxin against other bacteria) was identified in the island. This seems to support the idea that MW2 is really a community pathogen which is required to compete with other bacterial species for successful colonization to human mucous membranes without the help of antibiotics which MRSA strains in the hospital enjoy.

As exemplified as above, there are several allotypes for each Gisland, and the pathogenicity potential and antibiotic resistance profile of each *S. aureus* clinical isolate are determined as the sum of the function of all the Gisland allotypes possessed by the strain. This signifies the importance of Gisland allotyping as a rapid diagnostic method to infer the disease course and to determine therapy against the infection caused by individual *S. aureus* strain.[10]

Conclusion

After our publication of genome sequence information, the research targeting on the conquer of *S. aureus* infection has been tremendously accelerated. We are also trying our best in the same direction of efforts towards the development of new therapeutic and preventive measures for *S. aureus* infection.

Acknowledgement

I thank all the members of the National Institute of Technology and Evaluation and Research members for the Future Program of the Japan Society for the Promotion of Science

who were involved in nucleotide sequence determination of *S. aureus* genome. My special thanks go to all members of my lab in Tokyo especially to M. Kuroda, T. Baba, H. Yuzawa, T. Ito, K. Okuma, Y. Morimoto, Y. Katayama and F. Takeuchi.

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Hyperammonemia in Pediatric Clinics: A review of ornithine transcarbamylase deficiency (OTCD) based on our case studies

JMAJ 47(4): 160–165, 2004

Ichiro MATSUDA

Professor Emeritus, Kumamoto University

Abstract: Ornithine transcarbamylase, which is the enzyme to synthesize citrulline from carbamyl phosphate and ornithine, is located on the X chromosome. Male patients with OTCD present a wide clinical picture, as shown in the neonatal type (usually ending in death within one year) and the late-onset type (appearing between 2 and 56 years and characterized by long-term survival). OTC activity in the neonatal type is essentially undetectable, whereas those with the late-onset type have 8.1±6.3% of the control level. Mutations of male patients with the neonatal type (n=23) include base insertion/deletion, exon skipping, and nonsense and missense mutations. Mutations may lead to unstable mRNA or truncated protein, or involve the active site or cord domain of the enzyme, leading to structural changes. Mutations associated with the late-onset type (n=25) are only of the missense type, with most occurring on the surface of the enzyme. We performed prenatal monitoring for OTCD in 21 cases, among which one male fetus with Arg129His and two male fetuses with Arg40His (both belonging to the late-onset type) were diagnosed on the basis of gene analysis of amniotic cells. Treatment was initiated immediately after birth, enabling them to enjoy a normal school life. Two fetuses diagnosed as having neonatal-type mutations were terminated. Gene analysis provides the most reliable information about the future consequences of OTCD, especially in male patients.

Key words: Hyperammonemia; Urea cycle disorder; Ornithine transcarbamylase deficiency (OTCD); Genotype-phenotype correlation

Introduction

Hyperammonemia in children is observed in association with a variety of diseases and conditions including liver diseases accompanied with liver cirrhosis (e.g., congenital biliary atresia) and hereditary diseases such as urea-cycle enzyme defects, defective transport of ornithine

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 129, No. 1, 2003, pages 60–64).
This research was awarded the Medical Prize of the Japan Medical Association for 2002 in Clinical Medicine.

into mitochondria, and certain organic acidemias. In recent years, gene analysis of certain hereditary diseases has revealed the relationship between genotype and phenotype (the pathologic condition), and the results of analysis have come to be applied in clinical practice.

This paper describes ornithine transcarbamylase deficiency (OTCD), one of the most frequent of such hereditary diseases in Japan and the subject of our research since we reported the first case of this disease in Japan in 1971.[1)] Our group was the first to succeed in elucidating the structure of the OTC gene in 1988.[2)] In addition, identification of the carbamyl phosphate synthetase and arginase genes and elucidation of their mutant genes were also initially carried out by our group.[3–6)]

OTC, a urea cycle enzyme localized in mitochondria of the liver, is involved in synthesizing citrulline from carbamyl phosphate and ornithine. This enzyme is first synthesized as a precursor protein with a molecular mass of about 40,000 daltons in the cytosol, then transported to the mitochondrial matrix, where it is processed to the mature enzyme of about 36,000 daltons. It becomes active after being formed into a trimer. The OTC gene maps to Xp21.1 and is 73 kb long with 10 exons.[1)] OTC deficiency is an X-linked semidominant urea cycle disorder, and has the highest incidence (1 out of 50,000 people) among the various urea cycle disorders. Clinically, the age of onset is wide-ranging, involving infants to adults. The reason for such variety remained unclear until gene analysis provided relevant information.

Classification of Disease Types

About half of male patients (hemizygotes) have a neonatal onset, with the disease occurring within 1 month after birth; the other half experience late-onset disease. Most female patients (heterozygotes) have late-onset disease.[7)]

1. Neonatal-onset type

OTCD in neonates is severe and manifests with central nervous system (CNS) symptoms such as vomiting, spasm, coma, and lethargy, within 30 days after birth. In most cases, it ends in patient death within the first several months of life. Even if the patient survives, severe neurological disorders will remain. OTC activity in the liver is below the limit of detection.[7)]

2. Late-onset type

Late-onset disease occurs in patients of various ages, ranging from those in infancy, puberty, and adolescence, to middle age or even later. One patient had been known to be asymptomatic until the age of 65 years. Patients commonly lead a normal life until the onset of disease. However, some patients have been reported to have mild symptoms (vomiting and mild neural confusion) particularly when they have fever. Hepatic OTC activity in patients with normal IQ and normal electrocardiographic findings corresponds to $16.6 \pm 5.5\%$ of the normal level.[7)]

3. Female patients

Signs and symptoms vary widely among female patients (heterozygotes). Some are asymptomatic, while others eventually die after onset. Differences in the rate of inactivation of the X chromosome owing to lyonization are involved in how the disease manifests.[7)]

Relation between Disease Type (Phenotype) and Mutant Gene (Fig. 1)

Mutation of the OTC gene is basically individual, varying among those who are affected.[8)]

1. Gene mutation of neonatal-onset OTCD

About half the patients with neonatal-onset disease have nonsense mutations (mutations with a stop codon present in the sequence), base insertion, and base deletion. In this case, enzyme protein is always greatly decreased, and the activity level is virtually nil. The other half of patients have missense mutations (mutations accompanied with substitution of amino

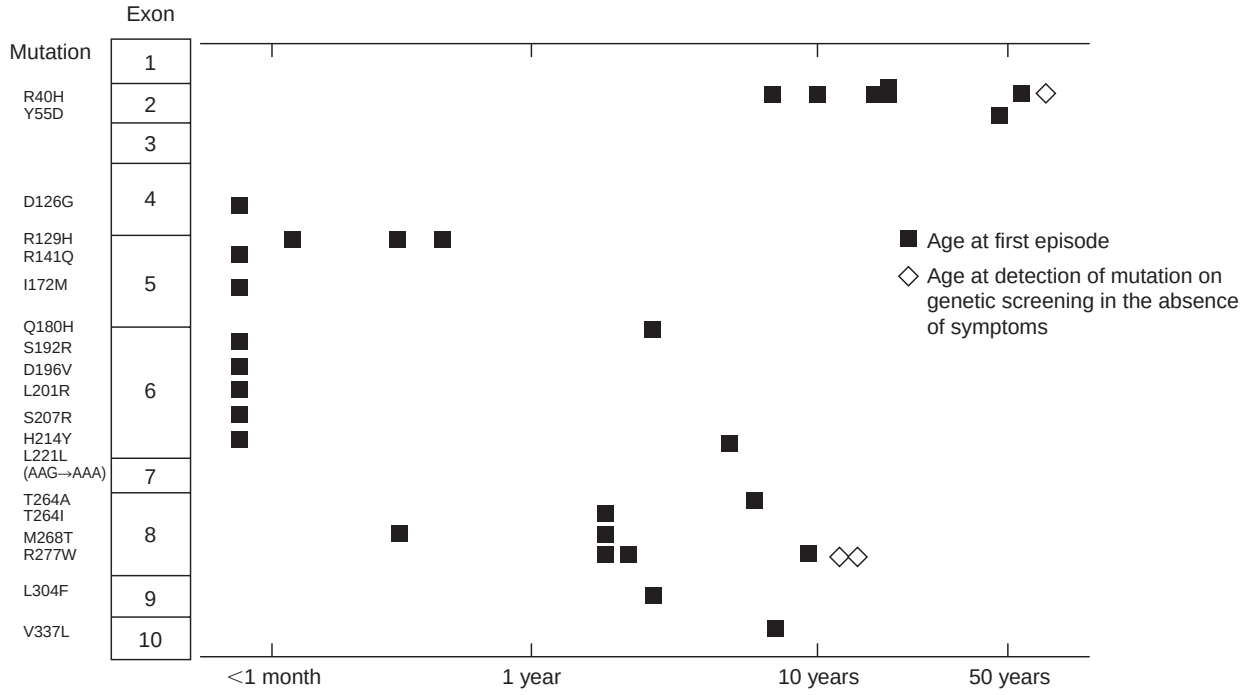

Fig. 1 Relationship between patient age at the first episode of OTCD and missense mutant genes
Mutations in patients who died within one month after birth (neonatal-onset disease) were located at the active site of the enzyme protein or at the site indispensable for composition of a trimer. Mutations in patients with late-onset disease were located on the surface of the enzyme protein.
(From Matsuda, I.: *Iden* 54; 2000: 48–54)

acids: e.g., D126G, R141Q, I172M, S192R, D196V, or L201R). All these mutations are missense mutations at sites important for enzyme activity, such as the site responsible for trimer formation and the active site of the enzyme.[8] In any case, OTC activity as examined in gene expression studies was below the limit of detection.[8,9]

2. Gene mutation of late-onset OTCD

In late-onset cases, all mutations are missense mutations, and most of them are located on the surface of the enzyme protein. The OTC activity corresponds to 10–15% of the normal level. Unlike neonatal-onset disease, identical gene mutations (R40H, R277W, R129H, M268T) are found in about 30% of the families of patients. The R4OH mutation, in particular, has been found in 6 families. In these families, there was a male patient who was 65 years old at the first examination and had never experienced episodes of hyperammonemia, as well as male patients who developed the disease at the ages of 9, 15, 17, and 48 years. The 65-year-old patient was found to have a daily protein intake of less than 65 g. Interestingly, the disease manifested in all these patients in the 1980s, when the protein intake among Japanese adult men reached about 80 g/day.[10]

3. Gene mutation of OTCD in females

In female patients, nonsense mutation, base insertion, base deletion, exon skipping, and missense mutation have been observed. However, mutations in female patients are basically of the same nature as those in male patients with neonatal-onset disease.[8]

4. Patient gender and carrier diagnosis

It is known empirically that the percentage

Table 1 Prenatal Diagnosis of OTCD

Case	Family	Specimen	Sex	Site of mutation targeted for diagnosis Exon/Intron	Mutation	Restriction enzyme	Result	Consequence
1	1	Villi	Male	Intron 1 (+4. A→C)		*Rsa* I	Patient	Aborted
2	1	Villi	Male				Normal	Continued
3	1	Villi	Female				Normal	Continued
4	2	Villi	Male	Exon 2 CGT→CAT	Arg 40 His	*Nla* III, *Mae* II	Patient	Continued
5	3	Villi	Male	Exon 2 CGT→CAT	Arg 40 His	*Nla* III, *Mae* II	Patient	Continued
6	4	Villi	Male	Exon 4 GAC→GGC	Arg 126 Gly	*Sdu* I	Patient	Aborted
7	5	Amniotic fluid	Male	Exon 4 CGT→CAT	Arg 129 His	*Msp* I	Patient	Continued
8	6	Villi	Female	Exon 5 CGA→TGA	Arg 141 Ter	*Taq* I	Carrier	Continued
9	6	Amniotic fluid	Female				Carrier	Continued
10	7	Villi	Female	Exon 5 CGA→CAA	Arg 141 Gln	*Taq* I	Carrier	Continued
11	7	Villi	Male				Normal	Continued
12	8*	Amniotic fluid	Male	Exon 6 AGC→AGG	Ser 192 Arg	*Pvu* II	Unevaluable	Continued (patient)
13	8	Villi	Male				Patient	Aborted
14	9	Amniotic fluid	Female	Exon 9 TGG→TGA	Ser 332 Ter	Base sequence analysis	Carrier	Continued
15	10	Amniotic fluid	Male	Intron 8 (+1. G→A)		*Msp* I, RFLP	Normal	Continued
16	11	Amniotic fluid	Female			*Msp* I, RFLP	Normal	Continued
17	12**	Amniotic fluid	Unknown				Unevaluable	Continued (patient)
18	13	Villi	Male	SSCP			(Normal)	Continued (normal)

*Maternal blood contamination **Bacterial contamination
SSCP: single-strand conformation polymorphism, RFLP: restriction fragment length polymorphism
(From Matsuda, I.: Ethical issues around prenatal diagnosis: From the standpoint of molecular biology. *Shusanki Igaku* 1998; 28: 999–1003. (in Japanese))

of carriers among mothers of male patients is not the same as that among mothers of female patients. Whereas 92% of mothers of male patients are carriers, fresh mutation was common in female patients, with only 20% of mothers of female patients being carriers.[11)]

Prenatal Diagnosis of OTCD

The author has been involved in prenatal monitoring for OTCD in 18 patients from 13 families (Table 1). The male-female ratio was 11:7. Four of the 7 females were carriers, and 6 of the 11 males had a mutant gene. Three of these 6 had late-onset OTCD, showing an R40H or R129H mutant gene. In these cases, treatment was begun just after delivery without abortion. The patients are currently in elementary school and are showing healthy growth. Three of the 18 cases underwent abortion after prenatal diagnosis.[12)]

Treatment and Prognosis

Administration of sodium benzoate or sodium phenylacetate is employed as pharmacotherapy, and a low protein diet (protein 1.0–1.5 g/kg/day plus essential amino acids at the required level) is used as nutritional therapy. However, since arginine is essential in this disease, in

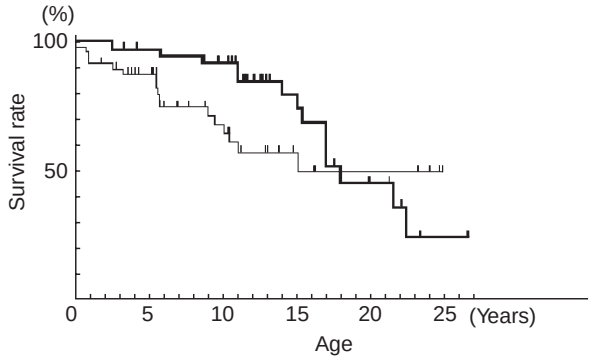

Fig. 2 Survival rate in patients with late-onset OTCD
Death of female patients (thin line) begins at about 5 years and follows a course similar to that in male patients (thick line). (From Uchino, T. *et al.*: Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan. *J Inherit Metab Dis* 1998; 21(Suppl 1): 151–159)

addition to the usual essential amino acids, arginine (400 mg/kg/day) should be given to the patient in conjunction with other essential amino acids.

With regard to prognosis, most neonatal-onset cases end in death within several months after birth, as mentioned previously. In contrast, male patients with late-onset disease and female patients show various courses of illness ranging from a complete lack of symptoms to death after the initial onset, under the strong influences of both the gene mutation (remaining enzyme activity) and treatment.[13] In general, patients with an initial blood ammonia level exceeding 1,000 μg/d*l* have a poor prognosis. Figure 2 shows the survival rate of Japanese patients.

In recent years, liver transplantation has been performed with the aim of radical treatment, achieving successful results in many cases. Although gene therapy is still in the experimental stage, AdexCAGhOTC, developed in Japan, has been demonstrated to be a considerably more efficient vector than AdexSR-αhOTC, developed in the US.[14] However, application to human subjects is not practical as long as basic immunological issues associated with adenovirus vectors remain unsolved.

Conclusion

In OTCD, gene mutations that severely affect the structure and function of OTC enzyme protein are associated with the complete absence of enzyme activity and neonatal onset, whereas gene mutations affecting the protein surface are associated with a 10–20% enzyme activity level and onset in late childhood or adulthood. In addition, a close association has been found between protein intake and disease onset. These findings represent a useful set of information for genetic counseling in relation to treatment of the patient and prenatal diagnosis of the disease.

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The Climacteric as a Crucial Stage of Female Life

JMAJ 47(4): 166–170, 2004

Yuji TAKETANI*, Tetsu YANO** and Koji KUGU***

*Professor and Chairman, **Associate Professor, ***Assistant Professor,
Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tokyo

Abstract: In women, the internal mileau undergoes relatively rapid physiological changes during puberty and at climacteric. Menarche and menopause are hallmarks of these two phases of female life, respectively, and changes of ovarian function account for these two events. The former event represents the appearance of ovarian function based on maturation of the hypothalamus, the control center for sexual function, whereas the latter event represents the termination of ovarian function secondary to ageing of the ovaries. During these two periods, women require particular attention to health care. Menopause gives rise to a variety of symptoms, because degenerative changes due to ageing are combined with a decrease of estrogen production due to reduced ovarian function. In a subset of women, treatment for menopausal symptoms has to be continued for a long period. Because the physical changes at menopause cannot be understood without complete knowledge of the action of estrogens, a thorough understanding of their systemic effects is mandatory. In addition, physiological changes secondary to the lack of estrogens should be discriminated from pathological changes so that appropriate medical intervention can be given in a timely manner for the latter. When these problems are solved, an ideal system for the support of ageing women may be established.

Key words: Life stage; Climacteric; Menopause; Estrogen; Climacteric syndrome

The Ageing Society

According to the 2001 abridged life tables, the average lifespan of Japanese men and women is 78.07 and 84.93 years, respectively, meaning that Japan has attained unprecedented ageing society in the world. Before World War II, the average lifespan for men and women was between 45 and 50 years, and women outlived men by two or three years. Subsequently, the average lifespan of women lengthened more rapidly than that of men. By

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 9, 2002, pages 1189–1191).

2000, the difference increased to about 7 years, so men aged 50 years and over made up 36.4% of the male population, while this rate was as high as 41.4% for women.

As the population ages, the need for medical care generally increases. Providing health care for middle-aged and elderly women is particularly important in the ageing society.

Life Stages of Women

In women, both body and mind are substantially influenced by sex hormones derived from the ovaries. The life of a woman can be divided into 6 stages, including childhood, puberty, sexual maturity, climacteric, menopause, and old age. The health management that women require and the diseases to which they are susceptible vary with the life stage because of the hormonal mileau and reproductive events that are characteristic of each stage, as well as changes due to ageing.

What Are the Climacteric and Menopause?

Climacteric is part of the ageing process, during which a transition occurs from the reproductive to the non-reproductive phases of life. Menopause is defined as the final cessation of menstruation secondary to the loss of ovarian function. A diagnosis of menopause is usually made retrospectively when spontaneous cessation of periods has occurred for one year between the ages of 45 and 55. The one-year period is necessary because menstruation or vaginal bleeding may occur sporadically within one year of cessation if ovarian function is not completely abolished. In fact, the ovaries of many women are able to produce hormones for 1–2 years after menopause, although the production is decreased compared with before menopause.

It has been reported that the average age of menopause is 51.3 years in the United States. In Japan, a study group of the Japan Society of Obstetrics and Gynecology investigated the occurrence of menopause in 3,591 women and reported that the average age was 49.7 years.[1)] The age of menopause varies little with race or the period of history. It is associated with genetic factors. Smoking and a slender physique are reported to be associated with a somewhat earlier menopause.

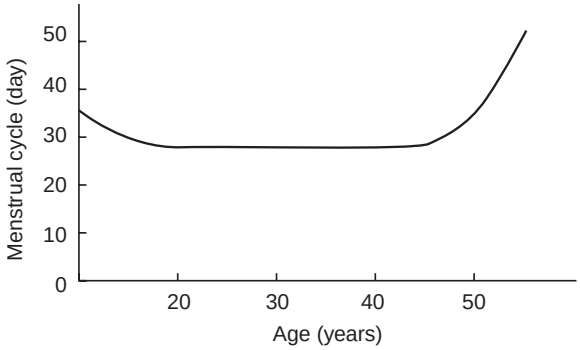

Fig. 1 Age and menstrual cycle

As stated above, the time of menopause can be specified, but the internal mileau does not change instantly at the time of menopause. Instead, gradual changes occur before and after menopause, while ovarian function declines slowly towards its termination. This transitional phase is defined as the perimenopause or climacteric. The latter term is derived from "klimax," which is a Greek word for ladder. This accurately expresses the characteristic endocrine changes in women around the time of menopause.

Endocrine Changes during the Climacteric

Typically, the menstrual cycle begins to lengthen about five years before menopause, before which menstruation has occurred regularly about every 28 days (Fig. 1). However, menopause occurs without prior lengthening of the menstrual cycle in about 10% of women. According to a survey performed in Japan, menstrual irregularity started before the age of 45 years, at 46 or 47 years, and at 48 or 49 years

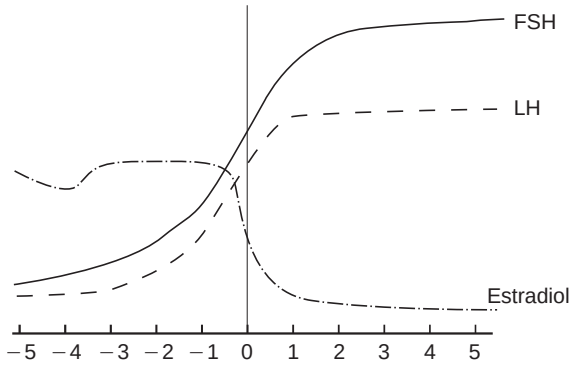

Fig. 2 Changes of hormone levels during the climacteric

Table 1 Age at the Onset of Various Climacteric Symptoms

	Average age	Standard deviation	*n*
Headache	50.4	4.85	286
Dizziness	50.6	4.68	148
Fatigability	50.8	4.69	388
Depressed mood	50.9	4.11	173
Irritability	51.0	4.42	218
Epigastric heaviness	51.0	4.57	119
Shoulder stiffness	51.2	4.97	449
Pruritis	51.2	5.10	204
Palpitations	51.2	4.63	178
Hot flushes	51.4	4.43	303
Insomnia	51.7	4.76	219
Low back pain	51.9	5.11	277
Sweating	52.0	4.55	258
Vaginal dryness	52.1	4.01	99

Subjects: 2,273 women aged from 40 to 65 years
Cited from: "Hiroi, M.: Reproduction and Endocrine Committee Report. Report of a questionnaire study on climacteric disorders in women from the general population. *Nichi Sanpu Zasshi* 1997; 49: 433–439."

in 15%, 30%, and more than 40% of women, respectively.[1)]

The levels of various hormones vary during the climacteric. First, the level of follicle-stimulating hormone (FSH) begins to increase progressively from 4 or 5 years before menopause. This change is preceded by a decrease in the blood levels of inhibin, which is secreted from the ovaries and inhibits pituitary secretion of FSH. Slightly increased FSH levels do not affect either the menstrual cycle or blood estradiol levels, but reflects the decline of reproductive function due to ageing. In other words, even if the cycle is normal, elevated FSH levels are suggestive of poor quality of oocytes. Under such conditions, fertility can be considered to show a substantial decrease. After elevation of FSH levels, LH levels also begin to increase from several years before menopause. An increase in LH levels is less marked than that of FSH (Fig. 2).

Regarding blood levels of estradiol, although the function of the ovaries (where estradiol is produced) begins to decline before menopause, its production is maintained because an increase of FSH offsets the decline of ovarian function. Estradiol levels are maintained, or are slightly increased in some cases, until about one year before menopause. At the time of menopause, both FSH and LH levels increase rapidly, but estradiol levels continue to decrease for a few years until it approaches the level similar to castration. Unlike estrogens, testosterone (a typical androgen) only decreases slightly after menopause. Androgen production by the adrenal glands decreases gradually with age, but persists for at least 10 years after menopause.

In postmenopausal women, low estrogen levels are mainly maintained by conversion of androgens in the peripheral adipose tissue. The more subcutaneous fat women have, the higher estrogen levels are.[2)] In obese women, the occurrence of climacteric symptoms is less frequent, and they have a relatively higher bone mineral density than in slender women, partly because of the production of estrogen by the adipose tissue.

Mental and Physical Changes during Climacteric

The reduction of estrogen production accounts for many of the biological changes during climacteric. There is overlap between changes

Table 2 Symptoms of Climacteric Syndrome

I.	Symptoms of autonomic dystonia
1)	Vasomotor symptoms: Feeling of warmth (facial hot flushes, and hot flushes), sweating, and sensitivity to cold
2)	Sleep disorders
3)	Others: Palpitations, headache, dizziness, and tinnitus
II.	Mental disorders
	Depression, mental lability, hypobulia, anxiety, and hypomnesia
III.	Other symptoms
1)	Locomotor symptoms: Shoulder stiffness, arthralgia, low back pain, and myalgia
2)	Gastrointestinal symptoms: Abdominal pain, anorexia, nausea, vomiting, and diarrhea
3)	Others: Fatigability, skin symptoms (eczema and pruritis), and dry mouth

Cited from: Sakamoto, M. *et al*. (Supervised and edited): *Principles of Obstetrics and Gynecology 1*, Revised edition. Medical View Co., Ltd., Tokyo, 2001, p. 690.

due to the loss of estrogen and other ageing processes. Various symptoms that appear during climacteric are called climacteric symptoms or climacteric syndrome. Climacteric symptoms are listed, with the frequency and average age of occurrence, in Table 1.[1)]

Climacteric symptoms can be classified as shown in Table 2.[3)] Vasomotor symptoms are most closely associated with the decrease of estrogen production, including hot flushes and sweating. In 10–25% of the female population, these two symptoms appear before menopause and they occur in 70–80% overall. At first, hot flushes develop during the night, and then in the daytime also. The onset is induced by stress. Hot flushes are frequently associated with sweating and palpitations. Their frequent occurrence during the night results in insomnia. Symptoms other than these vasomotor manifestations are associated with the personality, and with factors related to the family and society, which makes their pathogenesis complicated. Consequently, the incidence and symptoms of climacteric syndrome vary with the period of history and between countries. The commonest symptom in Japan is shoulder stiffness (Table 1).[1)] In Europe and the United States, however, the occurrence of this symptom during climacteric has almost never been described.

The decrease of estrogen levels gives rise to atrophic changes of the genitourinary tract. These changes appear after the manifestations of climacteric symptoms. In other words, vaginitis, vulvar pruritis, vaginal dryness, dyspareunia, urinary tract infection, and frequency occur several years after menopause. The skin also becomes thin and dry, which is considered to be caused by a decrease of cutaneous collagen fibers due to estrogen deprivation.

Estrogens are known to maintain and improve brain function. Although there is no conclusive evidence, it has been reported that estrogens can improve memory, and are effective for preventing Alzheimer's disease and suppressing its progression.

After menopause, bone mineral density decreases rapidly. Estrogen replacement therapy can prevent this decrease, and reduces the risk of fracture due to osteoporosis. In addition, estrogens are closely associated with lipid metabolism. The decrease of high density lipoprotein (HDL) cholesterol, as well as elevation of low density lipoprotein (LDL) cholesterol and total cholesterol, after menopause are mostly attributed to the decrease of estrogen levels.

Health Care for Postmenopausal Women

Women's health is more closely associated with biological and social factors than men's health. In particular, climacteric can be regarded as a transitional phase in which the internal and external mileau undergoes great changes and it is a crucial phase for women. It is important for women to change their health management methods and life goals to get along in good shape at the onset of the latter half of their lives. The decrease of female hormones at climacteric is dramatic. Medical specialists who play a role as healthcare providers must clearly understand the symptoms and pathological

conditions associated with climacteric, and must provide individual women with health care to improve their QOL and prevent diseases that particularly affect women undergoing menopause.

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Management of Depression in Late Middle Age

JMAJ 47(4): 171–174, 2004

Sueharu TSUTSUI

Professor, University of Human Arts and Sciences

Abstract: The etiologic factors and diagnostic hallmarks of involutional depression are described, together with points that should be taken into consideration when these disorders are treated by physicians other than psychiatrists. In order to diagnose depression in persons of late middle age, consideration of the socio-psychological factors that are often associated with involutional depression is important. It should first be clarified whether the patient has experienced loss of a relationship or social role, as well as the onset of lifestyle-related diseases. Changes of the living environment, such as building a new house or moving, may also induce depression. Although the presence of psychiatric symptoms like "depressed mood," and "anhedonia" is diagnostic, patients with depression often complain solely of physical symptoms, including anorexia, weight loss, fatigue, sleep disorders, and menopausal disorders. The physician who treats patients with involutional depression should ensure that he/she fully understands the characteristics of these disorders, and should prescribe appropriate rest and medication. Patients with depression occasionally attempt suicide. Consequently, physicians must know the signs suggesting the risk of attempted suicide. Patients who should be referred to psychiatrists are described here, as well as SSRI therapy and management of its side effects.

Key words: Loss experience; Lifestyle-related diseases; Sleep disturbance; Suicide

Introduction

According to international rankings of psychiatric conditions, depression was the fourth leading illness in 2000. In 2020, depression is projected to rise to the number 2 position. Women are more likely to suffer from depression than men and its lifetime prevalence is relatively high. Women are also susceptible to developing depression after the menopause. Unless depression is properly treated, patients may even commit suicide, so adequate care must be exercised when depression is managed.

This article deals with the etiology and clini-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 9, 2002, pages 1192–1194).

cal features of depression occurring after menopause, and also provides information on its management.

First, it should be emphasized that depression in postmenopausal women is likely to manifest with physical diseases, and such patients often present to clinics other than psychiatric clinics with various complaints. It is also not uncommon for organic diseases related to aging to be associated with depression in postmenopausal women.

Experience of Loss as a Common Cause of Depression

In postmenopausal women, careful investigation will reveal that depression can be related to stress derived from problems that are characteristic of this stage of life.

Depression in postmenopausal women is most commonly associated with loss of relationships or with the death of (or separation from) their spouse, siblings, relatives or other family members, friends, and acquaintances. In recent years, women have succeeded in achieving greater participation in public affairs. Like men, many women now play out their social role through their work. When such socially active women retire or change jobs, they experience loss of their social role and occasionally fall into depression. The decrease of physical and mental function due to aging, diseases such as cancer, and lifestyle-related diseases, as well as loss of confidence secondary to loss of physical attractiveness, may trigger depression. Loss of self-esteem is one of the background factors that must not be overlooked. In addition, financial loss and changes of living conditions (building a new house or moving, etc.) may also induce depression.

Symptoms that Suggest a Diagnosis of Involutional Depression

Symptoms characteristic of depression are listed in Table 1.

Table 1 Mental Symptoms Characteristic of Depression

- Decreased interest in daily affairs
- Depressed mood and suicidal ideation
- Feelings of guilt and emptiness of life
- Impaired social communication
- Feelings of powerlessness, desperation, and hopelessness
- Decreased concentration, stagnation of thinking, and loss of energy
- Self-accusation about inadequacy of ability
- Restlessness and increased anxiety

To diagnose depression, the presence of a "depressed mood" and "inability to feel pleasure and interest" are essential. Even if such psychiatric symptoms are not overt, they can be detected if the physician questions the patient. The symptoms that patients with depression complain of to gynecologists or general practitioners are mostly physical diseases. If depression is suspected, it is important to determine, without ignoring the presenting complaint, whether the patient also has any psychiatric symptoms characteristic of depression.

Agitated depression, which is characterized by severe anxiety and irritation, may occur in late middle age. Patients with this type of depression cannot keep still, showing restlessness of expression and behavior during history taking.

Patients in late middle age may present to clinics other than the psychiatric clinic with depression. If depression is suspected, it should first be confirmed whether they have a history of psychiatric disorders. Then, regardless of the presenting symptoms, it should be confirmed whether they have "anorexia," "weight loss," "discomfort when rising in the morning," "fatigability," and "sleep disturbance (awakening in the early morning, waking during the night, and a feeling of inadequate sleep). The diagnosis of depression is not covered here, so please see the published guidelines if necessary.[1)]

Management

1. Role of the physician

It is important for patients with depression to be given confidence that their condition can be cured by appropriate interventions. To achieve this, it is necessary for the physician and patient to trust each other. Because rest and adequate sleep are most important, arrangements to allow the patient to rest should be made. At the same time, the physician must ask the patient to definitely comply with drug therapy.

Because depression is associated with lack of energy, which is central to all aspects of life, it is important for the patients to avoid wasting energy as far as possible. Patients need a place where the atmosphere allows them to rest properly, should be left alone as little as possible, should be supported, should not be forced to do things that they find difficult, and should be provided with circumstances that allow them to seek relief from their disorders. The family members and other persons around the patient must be told that their cooperation is an indispensable part of the treatment. If they help to implement the therapeutic plan, the patient will recover faster.

When treatment is started, the disorders will initially improve slightly, but then will become worse again. Patients should be given confidence that eventually they will be cured. Also, the family should not put pressure on the patient, but should wait until the patient recovers his/her energy. If the patient relaxes and rests properly, uneventful recovery will follow.

2. Patients who should be referred to a psychiatrist

Depression of some types is better treated solely by psychiatrists and the patients who should be referred to psychiatrists are summarized in Table 2. As well as severe depression, agitated depression characterized by severe anxiety and irritation (which can occur in late middle age) is included among the indications for referral. In contrast, physicians can often control mild depression in a patient without any previous episode.

Table 2 Symptoms that Indicate a Need for Psychiatric Referral

- Severe cases: Refusal to eat, malnutrition, severe psychomotor retardation, or severe impatience or anxiety
- Poor compliance with therapy due to poor recognition of depression
- Risk of suicide
- History of recurrent depressive or manic episodes
- Persistent or intractable depression

If the patient is suicidal, psychiatric management is urgently required. When depression is associated with violent anxiety, impatience, intractable insomnia, uncontrollable aggressiveness, fierce self-accusation, or feelings of inadequacy, care must be taken to prevent the patient from attempting suicide. In Japan, 1,795, 1,820, and 1,791 women in late middle age (50 to 59 years old) committed suicide during 1998, 1999, and 2000, respectively.[2–4] About 30% of them left a suicide note, and the most common reason given for suicide was health problems, followed by either economic or family problems.

3. Drug therapy

In elderly persons[5] and women,[6] the antidepressants that are used most commonly for treatment of depression are selective serotonin reuptake inhibitors (SSRIs). In Japan, fluvoxamine and paroxetine are the available SSRIs. It is recommended to administer fluvoxamine or paroxetine at an initial dose of 25 or 10 mg/day, respectively, for one week, and then increase the dose gradually until the effective level is reached. This varies between patients, but is usually 75 to 100 mg/day and 20 to 30 mg/day, respectively.

SSRIs are known to have various adverse effects (Table 3),[7] among which nausea is the most common. Adverse effects are most likely to occur at the beginning of administration and

Table 3 Side Effects of SSRIs and Countermeasures

Side effects		Countermeasures and comments
Gastrointestinal	Nausea	• Transient nausea is often associated with higher doses. Administration should be started from a low dose. • Concomitant administration of mosapride citrate is effective.
	Anorexia	• Obese patients and those on a high carbohydrate diet are liable to develop anorexia.
	Diarrhea/soft stools	• Transient diarrhea or soft stools often occurs after administration of high doses.
Central nervous system	Increased anxiety	• Occurs soon after the initiation of drug therapy. • It is more likely to occur when anxiety is severe.
	Insomnia	• Concomitant administration of hypnotics that act on benzodiazepine-receptors.
	Tremor	• Tremor is alleviated when the dose is decreased. • Concomitant administration of β-blockers and anxiolytic agents.

Cited with modifications from "Brunello, N. *et al.*: Current understanding of the mechanism of action of classic and newer antidepressants. *Depression* 1994/1995; 2: 119–126."

their incidence increases when the starting dose is too high. Therefore, it is safer to start administration from a low dose.

To cope with nausea, antiemetic agents (5-HT_3 receptor antagonists) are administered with the antidepressant if necessary.

Involutional depression is frequently associated with lifestyle-related diseases. In such cases, SSRIs are also the first-line antidepressant agents. To treat insomnia, hypnotics such as zolpidem and brotizolam can be administered concomitantly for a while. Severe sleep disturbance is one of the risk factors for suicide, so sleep disturbance requires appropriate treatment.

Conclusion

Depression occurring in late middle age was described from a clinical standpoint. In addition to the causes and diagnostic features, the importance of appropriate treatment was emphasized. The points for consideration when depression is treated by physicians other than psychiatrists were also described.

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Atherosclerosis and Hyperlipidemia

JMAJ 47(4): 175–178, 2004

Masahiro AKISHITA

Department of Geriatric Medicine, Kyorin University School of Medicine

Abstract: It has been shown that the incidence of atherosclerotic disease such as coronary heart disease and stroke is lower in younger women than in men of the same age but increases after menopause, implying the athero-protective action of endogenous estrogen. In addition, observational studies have suggested the extensive efficacy of hormone replacement therapy (HRT) in postmenopausal women. The results of randomized controlled trials, Heart and Estrogen/Progestin Replacement Study and Women's Health Initiative, however, denied the effect of HRT on atherosclerotic disease. Taken the multiple actions of estrogen on atherosclerosis into consideration, including the effects on lipid metabolism and endothelial function, it is not likely that estrogen is ineffective at all. The safety and efficacy of HRT could be advanced by selecting the subjects and by developing the new regimen such as half-dose HRT and selective estrogen receptor modulators.

Key words: Estrogen; Coronary heart disease; Thromboembolism

Introduction

It has been shown that the incidence of atherosclerotic disease such as coronary heart disease and stroke is lower in younger women than in men of the same age.[1,2] The incidence, however, increases after menopause and comes up with age to the levels of men.[1,2] The prevalence of hyperlipidemia in women also increases after menopause and overwhelms that in men. These phenomena have been explained by the atheroprotective action of endogenous estrogen and its defect in postmenopausal women. Accordingly, it is supposed that hormone replacement therapy (HRT) can inhibit the progression of atherosclerosis in postmenopausal women, leading to the reduction of cardiovascular disease. In this short review, current indication of HRT to the protection of atherosclerosis in postmenopausal women is discussed.

Sex Difference and Postmenopausal Alteration of Atherosclerosis and Hyperlipidemia

A number of epidemiological studies have shown that the sex difference is apparent in the incidence of atherosclerotic disease. Figure 1A adapted from the Framingham Heart Study[1]

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 9, 2002, pages 1207–1209).

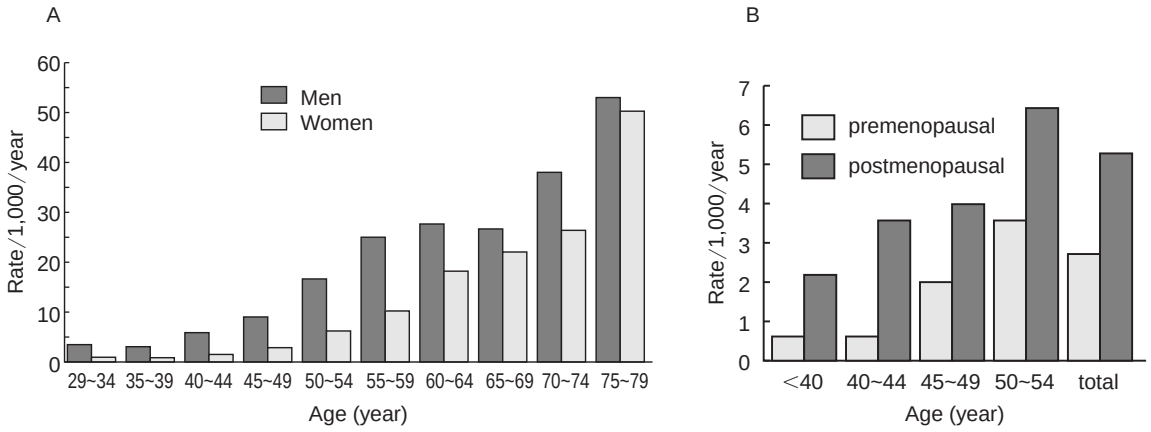

Fig. 1 Incidence of cardiovascular disease by sex and age (A), and by the menopausal status (B) (Adapted from the Framingham Heart Study, Ref.[1])

demonstrates that women <50 years have a lower risk (<50%) for cardiovascular disease than age-matched men. In contrast, the risk is increased in women after 50 years of age, and little sex difference can be found after 70 years. Similar epidemiological findings have been reported in Japan[2] although the incidence of cardiovascular disease is lower than in Western countries. The Framingham Study has examined the incidence of cardiovascular disease and the menopausal status in middle-aged women,[1] and has shown that postmenopausal women have a higher risk for cardiovascular disease than in age-matched premenopausal women (Fig. 1B), suggesting that menopause itself is a risk factor.

Many factors are attributable to the increase in atherosclerotic disease in postmenopausal women. Menopause is frequently accompanied by atherogenic risk factors such as hyperlipidemia, hypertension, obesity, and insulin resistance. In addition, vasoprotective actions of estrogen such as the stimulation of nitric oxide production[3] and inhibition of vascular smooth muscle cell proliferation[4] may play a role.

In Japan, the incidence of hyperlipidemia in postmenopausal women is 2–3 times higher than that in age-matched men, and the average plasma total cholesterol level in women of 50–59 years is approximately 230 mg/d*l* (data from the Ministry of Health, Labour and Welfare). In Japanese women, although total cholesterol as well as triglyceride is increased with age and by menopause, type IIa hyperlipidemia with the elevated LDL cholesterol level is dominant. Estrogen stimulates the activity of hepatic LDL receptor and increases the uptake of LDL cholesterol by the liver, resulting in the reduction of plasma LDL cholesterol levels. Also, through inactivation of hepatic triglyceride lipase, estrogen inhibits the conversion of IDL into LDL and hepatic uptake of HDL, resulting in plasma LDL cholesterol reduction and plasma HDL cholesterol elevation. Augmentation of hepatic and intestinal apo A-I synthesis by estrogen further contributes to the increase in HDL cholesterol production. The lowering effect of estrogen on plasma Lp(a) levels is important because statins do not have similar effects. Additionally, estrogen is known to inhibit the oxidation of LDL cholesterol.

Indication of HRT to Atherosclerosis and Hyperlipidemia

A number of observational studies have shown that HRT users have a lower incidence of atherosclerotic disease than nonusers. The relative risk was approximately 0.5 (Table 1),[5] supporting the anti-atherosclerotic action of

Table 1 Adjusted Risk of Death Among Postmenopausal Hormone Users in the Nurses' Health Study, 1976–1994 (Adapted from Ref.[5])

Cause of Death	Hormone Use		
	Never	Current	Past
All causes	1.0	0.63	1.03
Coronary heart disease	1.0	0.47	0.99
Stroke	1.0	0.68	1.07
All cancer	1.0	0.71	1.04
Breast cancer	1.0	0.76	0.83

Table 2 Indication of HRT to Atherosclerosis and Hyperlipidemia
(Adapted from "HRT Guidelines for the Health Promotion of Elderly Women" Ref.[8])

- Initiation or continuation of HRT in postmenopausal women for whom the potential benefits may exceed the potential risks, considering the atherosclerosis risk factors and complications.
- When the patient has climacteric disorder or osteoporosis, and thus HRT may be indicated but she has mild hypercholesterolemia, hypertension or diabetes mellitus, these atherosclerosis risk factors may be followed-up for a few months. No improvement with HRT or moderate-to-severe atherosclerosis risk factors should be treated by their primary interventions.
- When the patient does not have climacteric disorder or osteoporosis, HRT should not be indicated for treatment of atherosclerotic disease or atherosclerosis risk factors.

estrogen. Heart and Estrogen/Progestin Replacement Study (HERS),[6] a large-scale randomized placebo-controlled secondary prevention trial in postmenopausal women with coronary heart disease, was reported in 1998. However, during the follow-up period of average 4.1 years, 0.625 mg/day of conjugated equine estrogens plus 2.5 mg/day of medroxyprogesterone acetate, standard regimen of HRT, failed to exert the protective effect against the new occurrence of coronary events. Furthermore, Women's Health Initiative (WHI), a large-scale primary prevention trial, reported in 2002 that HRT increased the relative risks for coronary events and stroke to 1.29 and 1.41, respectively.[7] These results have raised the question about the efficacy of HRT. The concern is that the thrombogenic effect of estrogen through the coagulation/fibrinolysis system would overcome the anti-atherogenic effect such as the improvement of lipid metabolism and endothelial function. Based on the opinion that progestin that is used to prevent myometrial cancer might be harmful, or the dose of regular HRT could be too much, the development of new regimens have been in progress. For the prevention of atherosclerosis, the development of selective estrogen receptor modulators (SERM) is ongoing and anticipated.

"HRT guidelines for the health promotion of elderly women," published in 2001,[8] summarized the indication of HRT to atherosclerosis and hyperlipidemia as Table 2. Although the guideline appears complicated, it describes the importance that the indication should be decided individually based on the overall status of the patients but should not be decided by the disease only. Given the results of WHI, the amendment may not be necessary in Table 2, but the regimen of HRT such as dose should be improved. When the patient's risk for atherosclerotic disease is estimated to be high, half-dose HRT will be better to reduce the risk for thromboembolism.

Conclusion

Previous observational studies suggested the extensive efficacy of HRT including coronary heart disease in postmenopausal women. The results of randomized controlled trials, HERS and WHI, however, denied the effect of HRT on atherosclerotic disease. Taken the multiple actions of estrogen on atherosclerosis into consideration, it is not likely that HRT is ineffective at all; the improvement of plasma lipids by HRT was reproducible in HERS and WHI. Consequently, the safety and efficacy of HRT can be advanced by selecting the subjects and by developing the new regimen such as half-dose HRT and SERM.

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Osteoporosis
—Clinical aspects of hormone replacement therapy—

JMAJ 47(4): 179–182, 2004

Yasufumi HAYASHI

Tokyo Metropolitan Geriatric Hospital

Abstract: Because of a rapid decrease in the concentration of serum estrogen, which maintains bone mineral density in women, the bone mineral density of postmenopausal women decreases by about 20% during the first 10 years after menopause. The rate of decrease in bone is easily determined by measuring bone metabolic markers. Bone resorption markers consist of deoxypyridinoline and cross-liked N-telopeptide, and they serve as predictors of progression of bone loss. Hormone replacement therapy is effective in increasing the bone mineral density of postmenopausal women, whose levels of bone resorption markers are usually high. However, because of fear of adverse effects of estrogen, such as breast cancer or uterine cancer, hormone replacement therapy is not popular, with only one percent of postmenopausal women being continuously given estrogen in Japan. By contrast, raloxifene, a selective estrogen receptor modulator that will be available to Japanese physicians in the near future, is effective in strengthening bones and reducing serum cholesterol, but does not stimulate the sex organ function. Raloxifene will become the method of the first choice for promoting the quality of life of osteoporosis patients through prevention of breast cancer and cardiac diseases in postmenopausal women.

Key words: Menopause; Osteoporosis; Hormone replacement therapy (HRT); Bone metabolic markers

Menopause and Osteoporosis

Osteoporosis, a condition characterized by reduced bone mineral density, is inevitably associated with menopause and involves organs other than the genital tract. Ohsawa and Okano *et al.* investigated the changes in the bone mineral density in 176 healthy perimenopausal women at intervals of 12 months twice by DXA (dual energy x-ray absorptiometry), using a QDR 1000W. They reported that the time-course of changes in the bone mineral density

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 9, 2002, pages 1210–1211).

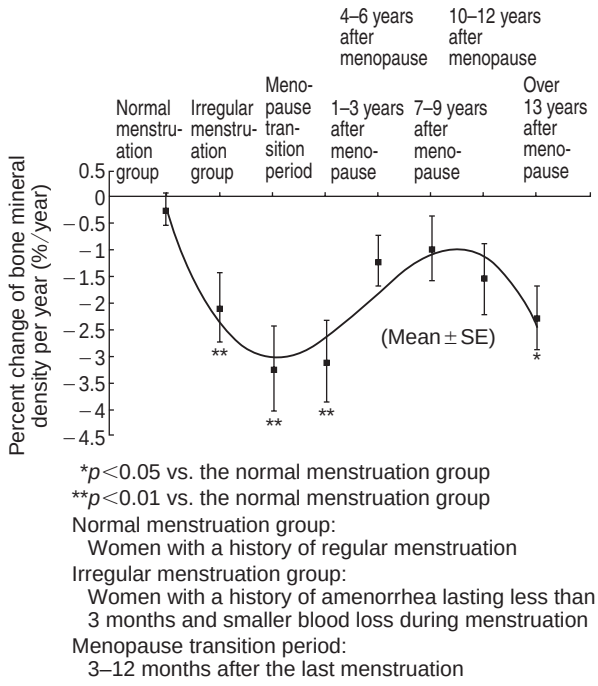

Fig. 1 Relationship between perimenopausal stage and annual percent change of bone mineral density[1)]
(Ohsawa, M. *et al.*: Age-related changes in bone metabolism of postmenopausal women. *Osteoporosis Japan* 2000; 8: 56–58)

could be depicted by an S-shaped curve, as shown in Fig. 1. They found that the bone mineral density remained almost unchanged during the survey period in the normal menstruation group, whereas in the irregular menstruation group, the density decreased by 2% each year; furthermore, they noted a 3% or greater decrease of bone mineral density annually during the transition period to menopause and during the first 1–3 years after menopause. The annual rate of decrease of the bone mineral density dropped to about 1% by seven to nine years after menopause, and increased again to about 2% after the 9th year of menopause.[1)]

Thus, the bone mineral density decreased markedly immediately after menopause and decreased by a total of about 20% during the first ten years after menopause. It is known that postmenopausal decrease of bone mineral density is associated more with accelerated bone resorption than with reduced bone formation.

Two markers of bone metabolism in the urine that are measured to evaluate the degree of bone resorption are covered by the Health Insurance System in Japan: (1) cross-linked N-telopeptide (Osteomark®, abbreviated as NTx), and deoxypyridinoline (D-Pyr). It has been reported that the urinary D-Pyr level increases about 15% at postmenopausal period compared with premenopausal period, that bone mineral density decreases by 2% or more annually in women whose urinary Osteomark® level measured at the time of menopause is within the highest quarter (1/4) of the range, and that the bone mineral density remains unchanged in women whose urinary Osteomark® level at the time of menopause falls in the lowest quarter of the range. It has also been shown that when women were divided according to the urinary Osteomark® level measured at the time of menopause into four quarter groups, the percent increase of bone mineral density following hormone replacement therapy (HRT) was more than two fold in the highest quarter group as compared to that in the lowest quarter group. These findings indicate that measurement of these bone metabolic markers can be used for selecting the optimum therapy for individual patients.

In women who show accelerated bone resorption resulting in reduced bone mineral density following menopause, a diagnosis of osteoporosis is made if at least one of the following three criteria is satisfied[2)]: (1) fracture of a vertebral body or metaphysis of a long bone in the absence of significant extrinsic force; (2) decrease of bone mineral density to a level equivalent to 70% or lower than that in younger individuals; (3) signs of osteoporosis in radiographs (coarseness or complete absence of longitudinal bone trabeculae within the thoracic or lumbar vertebral bodies).

Expected Effects of Hormone Replacement Therapy

It has been known for many years that estro-

gen deficiency associated with menopause is associated with reduced bone mineral density and osteoporosis. Hormone replacement therapy (HRT) for osteoporosis has been practiced for over 20 years. At first, estriol was used, but this agent was reported to be slightly inferior to active vitamin D_3, which exerts excellent bone-mineral-density-elevating activity. This unsatisfactory initial result of HRT was considered to be attributable, in general, to the poor nutritional status of the Japanese people, as a whole, in the olden days.[3] In recent years, conjugated-type estrogens, which exhibit higher efficacy as compared to previous hormone replacement regimens, have been used for HRT.

As described above, the efficacy of HRT for osteoporosis is affected by the degree of postmenopausal acceleration of bone resorption. When patients were divided into four quarter groups by the urinary levels of bone metabolic markers, the percent increase of the bone mineral density per year following HRT was determined to be 1% in the lowest quarter group, and 4% in the highest quarter group (2% overall). Thus, it would be reasonable to state that HRT provides a reliable means of increasing the bone mineral density, similar to bisphosphonate therapy. In Japan, however, only about 1% of all women in the menopausal age group receive treatment for osteoporosis. This low percentage may be attributable to the following factors: (1) prophylactic therapy aimed at preventing a decrease of bone mineral density is unfamiliar to Japanese women; (2) Japanese women are highly concerned about the increased risk of breast and uterine cancer associated with HRT; (3) Japanese women are concerned about the adverse reactions of HRT, such as uterine bleeding and breast tension.

To resolve these concerns which have interfered with the spread of HRT, a selective estrogen-receptor modulator (SERM), which does not act on the uterus or mammary glands, was developed. This drug, called raloxifene, is expected to become available commercially within one year. When this drug was used at a low dose level (60 mg/day) in women without vertebral fracture, the incidence of new fractures was reduced to about 1/10 of that in untreated women with existing vertebral fracture (Fig. 2).[4] This result suggests that prophylactic low-dose raloxifene therapy may reduce to the number of patients suffering from fractures to about 1/10th of that among untreated patients; additionally, it also reduces the serum cholesterol level, and the incidence of breast cancer to about 2/3 of that in untreated women. This drug is thus promising not only for the treatment of osteoporosis, but also for reducing the incidence of such events as myocardial infarction, stroke, and dementia.

In the near future, HRT for osteoporosis may be expected to spread widely, not only allowing the bone strength of women in the postmenopausal age group to be reinforced, but also facilitating preservation and improvement of other physical functions of women.

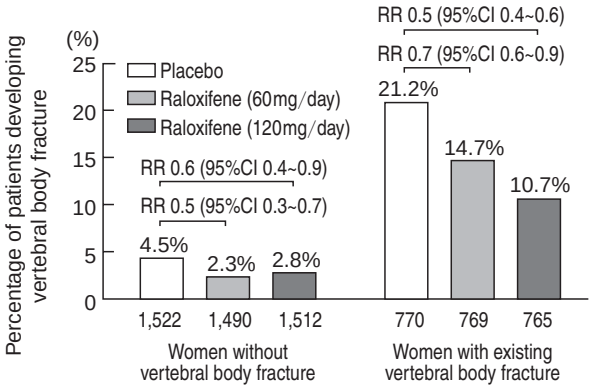

Fig. 2 Effects of raloxifene in suppressing vertebral body fracture

Early treatment with this drug in women without fracture reduced the incidence of vertebral body fracture to about 1/10 of that in untreated women with existing fracture. (Three-year MORE study by Ettinger, B. *et al.*: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: result from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA 1*999; 282: 637–645)

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Disorders of the Urogenital Organs

JMAJ 47(4): 183–185, 2004

Takeyoshi OHKURA

Professor, Department of Obstetrics and Gynecology,
Koshigaya Hospital, Dokkyo University School of Medicine

Abstract: Estrogen receptors are densely distributed in the trigone of the urinary bladder, the urethra, and the vagina, all of which are structures that develop from the urogenital sinus. Consequently, chronic postmenopausal estrogen deficiency affects the urogenital tissues and causes atrophy that leads to dysfunction of the urogenital organs. In this article, the clinical effects of hormone replacement therapy (HRT) on menopausal or geriatric urogenital dysfunction are described along with the relevant pathophysiological background.

Key words: Estrogens; Urinary tract infection; Urinary incontinence; Coital disorders

Introduction

Chronic estrogen deficiency occurs after the menopause and this affects the urogenital tissues, causing atrophy, because estrogen receptors are densely distributed in the trigone of the urinary bladder, the urethra, and the vagina, all of which develop from the urogenital sinus. Consequently, postmenopausal estrogen deficiency is a cause of various types of urogenital dysfunction.

In this article, the clinical effects of hormone replacement therapy (HRT) on urogenital dysfunction during the menopausal or geriatric periods of female life are described together with the pathophysiological background.

Clinical Effect of HRT on Urinary Tract Dysfunction

1. Urinary frequency, nocturia, urgency, and urinary tract infection

After the menopause, chronic estrogen deficiency leads to urethral atrophy, and even in the absence of urinary tract infection, frequency, nocturia, urethral burning, and urgency can occur along with dysuria.[1)] As the urethral mucosa becomes thinner, the sensory nerves come closer to the mucosal surface. Consequently, the passage of urine stimulates these nerves through the thin mucosal epithelium and produces a burning sensation.[2)] Postmenopausal urination problems are characterized by difficulty in initiating micturition, partly because of atrophy of the distal urethra. In addition,

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 9, 2002, pages 1212–1213).

Table 1 Alterations in Vaginal Flora and pH in the Two Groups*

Variable	Estriol Group (N = 36)	Placebo Group (N = 24)
Positive vaginal cultures — No. (%)		
Pretreatment		
Lactobacilli	0	0
Enterobacteriaceae	24 (67)	16 (67)
After 1 mo of treatment		
Lactobacilli	22 (61)	0†
Enterobacteriaceae	11 (31)	15 (63)‡
After 8 mo of treatment		
Lactobacilli	21 (58)	0†
Enterobacteriaceae	10 (28)	17 (71)‡
Vaginal pH		
Pretreatment	5.5 ± 0.7	5.8 ± 1.2
After 1 mo of treatment	3.8 ± 0.8	6.2 ± 1.2†
After 8 mo of treatment	3.6 ± 1.0	6.1 ± 2.0†

*Only women who had cultures at the one- and eight-month visits were included in the analysis. Plus–minus values are means ± SE.
†$p<0.001$ for the comparison between groups.
‡$p<0.005$ for the comparison between groups.
(Raz, R. and Stamm, W.E.: *N Engl J Med* 1993; 329: 753–756)

atrophy lowers the threshold to stimulation and makes the urethra vulnerable to injury, rendering the urinary tract susceptible to ascending infection.[1)]

The vaginal bacterial flora are altered secondary to an increase of pH due to the disappearance of lactobacilli, inducing the migration of enterobacteriaceae (particularly E. coli) into the vagina. The subsequent proliferation of these organisms, as well as urethral atrophy, contribute to the occurrence of postmenopausal urinary tract infection.[1)]

Urinary tract infection is recurrent in 8% to 10% of the female population over the age of 60 years.[3)] Antibiotic therapy for 3 days followed by application of a vaginal cream containing estriol (E_3) can improve the vaginal pH, and is markedly effective against such recurrent urinary tract infection (Table 1).[3)] Like vaginal cream, oral E_3 is also effective. Estrogens are effective because they restore vaginal autopurification, and prevent the entry of enterobacteriaceae into the introitus and their subsequent proliferation, through 1) revitalization of the atrophic vaginal and urethral mucosae, and 2) acidification of the intravaginal pH secondary to increased proliferation of lactobacilli.

2. Urinary incontinence

Urinary incontinence does not suddenly increase after the menopause, but it increases with age until the sixth decade of life.[4)] Furthermore, it is significantly more common in multiparous women than in nulliparous women. Estrogen replacement therapy (ERT) is effective for urge incontinence, but estrogen therapy alone is ineffective against urinary incontinence due to increased abdominal pressure (stress incontinence).[5)] A combination of estrogen and an α-adrenergic receptor stimulant is more effective than either agent alone.

The major causes of stress incontinence due to increased abdominal pressure include laxity of the muscles and tissues forming the pelvic floor, and weakening of the supporting tissues of the bladder. In addition to the drugs described above, training to strengthen the muscles of the pelvic floor is an essential part of conservative therapy for stress incontinence.

Clinical Effects of HRT on Symptoms of the Reproductive Organs

1. Diseases of the vagina and external genitalia

Local or systemic administration of estrogens is markedly effective for atrophic vaginitis (senile vaginitis). Unlike vaginitis, vulvar dystrophies which are caused by the loss of subcutaneous fat and elasticity resulted from menopause are poorly responsive to ERT, because vulva is not a Müllerian derivative.[6)]

2. Sexual dysfunction

Postmenopausal atrophy of the vagina and surrounding tissues due to estrogen deficiency prevents vaginal dilation in response to sexual

stimulation and reduces lubrication. This causes pain during intercourse (dyspareunia). Postmenopausal vaginal atrophy is less severe in women who are sexually active (intercourse 3 times or more per month) around the menopause than in women who are sexually inactive (less than 10 times per year). In addition, sexually active women find intercourse less uncomfortable than sexually inactive women.[7)]

Semmens *et al.* assessed physiological changes such as the intravaginal pH and vaginal blood flow in postmenopausal women receiving HRT for 24 months.[8)] This study showed that HRT significantly improved both the intravaginal pH and vaginal blood flow after one month. In particular, vaginal blood flow continued to increase throughout treatment for 24 months. HRT does not directly stimulate sexual desire, but can indirectly benefit sexual function and hence improve the quality of life (QOL).

Conclusions

Postmenopausal dysfunction of the urogenital organs secondary to chronic estrogen deficiency is unavoidable for all women, although the severity varies among individuals. Such dysfunction can markedly worsen the QOL of postmenopausal women. By using HRT, or oral or transvaginal E_3 preparations that rarely cause side effects, many of the symptoms of dysfunction can be considerably alleviated. Accordingly, these therapies are considered useful for improving QOL in postmenopausal women.

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Risk Factors for Prostate Cancer

JMAJ 47(4): 186–191, 2004

Osamu OGAWA

Professor, Department of Urology, Kyoto University Graduate School of Medicine

Abstract: Prostate cancer is one of the representative cancers that show a marked difference in morbidity by race and region. In the U.S.A., the annual frequency for the diagnosis of prostate cancer is ranked first among all cancers excluding skin cancer, and it is the second leading cause of death following lung cancer. Meanwhile, the incidence of prostate cancer in Asian countries, including Japan, is considerably low. It is actually reported that the difference in incidence between African Americans, showing the highest prevalence, and the Japanese, is at least ten times. Based on epidemiological information, it is speculated that the long-term exposure to certain environmental factors, including diet, acts as a risk for prostate cancer. Certain genetic factors also participate. Recent epidemiological studies on human cancer not only demonstrate the risk factors for cancer, but also greatly contribute in illuminating the processes of carcinogenesis, enabling the identification of highly suspected groups of carcinogens, and finally, establishing an effective strategy of preventive measures against cancer. In the control of prostate cancer, the identification of risk factors and the promotion of active preventive medicine can provide enormous benefits to the super-aging society of our future.

Key words: Prostate cancer; Epidemiology; Environmental factors; Genetic factors

Introduction

External environmental factors have a large influence on the development of human cancers. If all carcinogenic environmental factors could be eliminated, 90% of all cancer would probably be preventable.[1)] Meanwhile, host susceptibility to the carcinogenic environmental factors is influenced by various factors such as gender, age, nutritional state, and genetic factors. If it is possible to identify the carcinogenic environmental factors and to estimate their susceptibility to external factors, it would appear that cancers could effectively be prevented by combining various approaches.

Cancer epidemiology is a classic scientific approach of investigating clues involving external environmental factors. The types of approach

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 9, 2002, pages 1250–1254).
The Japanese text is a transcript of a lecture originally aired on June 20, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

in cancer epidemiology include descriptive and analytical epidemiology. The former examines the morbidity, mortality, etc., and draws various conclusions based on examination, while the latter analyzes the relationships between certain diseases and various factors that are thought to contribute to the disease. In this review, I would like to explain the risk factors for prostate cancer from an epidemiological point of view by looking at recent descriptive epidemiological trends concerning prostate cancer, secondly, at external factors involved in prostate cancer, based on analytical epidemiology, and finally, at overall features concerning the risk factors for prostate cancer introducing research on genetic factors.

Table 1 Prostate Cancer and Dietary Factors

Factors that can increase risks
Total calorie intake (obesity)
Saturated fatty acids
Factors that may decrease risks
Soy protein
Isoflavonoid
Fruit, Vegetables
Vitamin A (lycopene)
Vitamin E
Vitamin D
Selenium
Green tea
Catechin

Descriptive Epidemiological Trends Concerning Prostate Cancer

Prostate cancer is one of the representative cancers that shows a marked difference in morbidity by race and region. In the U.S.A., the annual frequency for the diagnosis of prostate cancer is ranked first among all cancers excluding skin cancer, and it is the second leading cause of death following lung cancer. An epidemiological survey of prostate cancer in the U.S.A. in 2001 reported 31,500 deaths, while 198,100 patients were newly diagnosed.

Meanwhile, the incidence of prostate cancer in Asian countries, including Japan, is considerably low. It is actually reported that the difference in incidence between African Americans, showing the highest prevalence, and the Japanese is at least ten times. Further, from 1988 to 1992, the age-adjusted mortality rate of prostate cancer was only four per 100,000 of the population for Japanese, compared with 36, the highest rate, in African Americans. In recent years, however, the prevalence of prostate cancer shows a tendency to increase regardless of high or low incidence regions. The cancer statistics white paper for 1999 shows that the actual mortality of prostate cancer in Japan was 7,005 in 1999, and is expected to be 15,801 in 2015, and it would consequently ascend to the seventh place for cancers in males, ranking under esophageal and rectal carcinomas.

Another characteristic of prostate cancer is that the prevalence increases with age. The morbidity/mortality rate increases exponentially with age.[2)]

Risk Factors of Prostate Cancer Based on Analytical Epidemiology

As mentioned above, the descriptive epidemiological data accumulated up to the present shows that only age and race (regional difference) are established as risk factors for prostate cancer. Based on the epidemiological information, it is speculated that long-term exposure to certain environmental factors, including diet, acts as a risk for prostate cancer. Certain genetic factors also participate.

1. Dietary factors (Table 1)

(1) **Fat intake**

In general, fatty acids are classified as saturated or unsaturated. Of these acids, it seems that saturated fatty acids, which are mostly found in animal fats, enhance the risk for prostate cancer, and several case-control studies

have reported a significant association between a high intake of saturated fat and prostate cancer. However, in a recent cohort study that compensated for caloric intake, no significant relationship was detected although a tendency for the risk to increase was recognized. Kolonel *et al.* reviewed the previous epidemiological studies, and reported that the relationship between the intake of saturated fatty acids and prostate cancer had been suggested in many case-control studies. They also inferred that the rate at which excessive intake of saturated fatty acids contributed to the incidence of prostate cancer was 20 to 25% for European Americans and African Americans and 5 to 10% for Asian Americans.[3)]

(2) **Soy protein**

Isoflavonoid, which is mostly found in soybeans, has an estrogenic structure. It has also been assumed that isoflavonoid probably suppresses prostate cancer because the morbidity of prostate cancer is low in several South-East Asian countries where soy protein is ingested in large amounts. Soybeans contain two kinds of isoflavonoids, namely genistein and daidzein. Nagata *et al.* suggested that the ingestion of soybean products cause a decrease in the sex hormone concentration in the blood of Japanese males. They speculated that this influence on the sex steroid may be one of the mechanisms involved in preventing the development of prostate cancer.[4)]

(3) **Vegetable, fruit, and the vitamins they contain**

It has been proposed that vitamins contained in vegetables and fruit prevent carcinogenesis. However, the relationship between vegetable and fruit ingestion, and prostate cancer has not been clearly established.

It is suggested that vitamin A and such precursors as retinol and carotinoid, protect against oxidative stress, thus suppressing carcinogenesis. Of these, β-carotene and lycopene have most widely been studied for their relation to prostate cancer. Oishi *et al.* conducted a study into the relationship between β-carotene ingestion and prostate cancer, and reported that the relative risk for prostate cancer is significantly increased at lower ingestion levels of β-carotene compared to higher ingestion levels.[5)] However, no uniform tendency was demonstrated in later reports. Lycopene is mostly found in tomatoes, and has been proven to have an inhibitory effect on the proliferation of prostate cancer cells *in vitro*. A recent report suggested a meaningful inverse correlation between lycopene concentrations in the blood and prostate cancer.[6)] Although vitamin E is also considered to suppress carcinogenesis due to its strong antioxidant activity, there are no definite reports indicating a significant association with the prevention of prostate cancer.

Taking all the above facts into consideration, at this point there is no conclusive evidence that clearly supports the preventive effect of vitamin A and E on prostate cancer. However, it is considered necessary to further investigate the possible preventive effect of lycopene and vitamin E on the development of prostate cancer.

(4) **Vitamin D**

Insufficient exposure to sunshine (ultraviolet rays) has a significant association with a high prostate cancer morbidity, and an inhibitory effect of active vitamin D on the development of prostate cancer has been suggested. Actually, active vitamin D (1,25 vitamin D) shows a suppressing effect on the proliferation of prostate cancer cell lines. Additionally, the existence of vitamin D receptors on prostate cancer cells has been proved.

(5) **Selenium**

Selenium is a metal element similar to sulfur, and is found in large amounts in plants that grow in soil and take nutrients from the soil. Recently seven prospective studies reported a possible relation between the prostate cancer risk, and the quantity of selenium in the blood or nails. Of these, two studies reported a significant relationship, while three studies showed a preventive effect of selenium, even though a significant relationship was not demonstrated.

Based on these studies, selenium is expected to show a preventive effect against prostate cancer. At present, a prospective cohort study investigating the effect of chemical prevention by using selenium and vitamin E is being conducted in the U.S.A.[7)]

(6) **Green tea**

One of the differences in dietary habits between Asian and Western countries is the amount of green tea consumed in Asia. The apparent anti-tumor effect of green tea is based on catechin, a polyphenol. Experiments on prostate cancer cell lines have shown that catechin has a suppressing effect on cell proliferation, and a recent large-scale cohort study in Japan reported that the intake of at least 10 cups of green tea a day may cause a delay in the clinical onset as well as a decrease in the prevalence of cancers.[8)] Even though there is still no definitive evidence that green tea reduces the risk for developing prostate cancer, green tea is an attractive candidate for use in the prevention of prostate cancer since it is rarely toxic and is readily acceptable as a dietary ingredient.

2. Benign prostate hyperplasia

During the past 30 years, there has been controversy over the relationship between benign prostate hyperplasia and prostate cancer. Like prostate cancer, benign prostate hyperplasia is an age-dependent condition that is evidently related to sex hormones. The weight of the prostate glands of males in Asian countries is smaller than that of Western males, even after correction for physique. There may be a cofactor, e.g. a gene, that exists both in hyperplasia and cancer. However, benign prostate hypertrophy and prostate cancer develop in anatomically different regions of the gland. That is, benign prostate hyperplasia occurs in the central region surrounding the urethra, called the transition zone, whereas approximately 70% of prostate cancers develop in the peripheral zone, closer to the rectum. Also, recent molecular studies have failed to show that benign prostate hyperplasia and prostate cancer share the same genetic base. Summarizing the above facts, though there may be some cofactors that cause both benign prostate hyperplasia and prostate cancer, it is reasonable to say that there is no clear relationship between them.

3. Drinking and smoking

Concerning the relationship between prostate cancer and non-essential substances like alcohol, cigarettes etc., there have been many negative reports. Dennis *et al.* reported interesting results of their meta-analysis investigating the relationship between prostate cancer and alcohol intake.[9)] According to their review, a significant relationship was not recognized in the overall analysis, but appeared as the alcohol intake increased. This result may agree with the report by Tonnesen *et al.* describing a relationship between prostate cancer and alcohol dependency.[10)] Therefore, it is assumed that excessive drinking may act as a risk factor for prostate cancer.

4. Sex hormone

Androgens are essential to the development of a normal prostate. Further, since the proliferation of prostate cancer cell shows androgen dependency, it is assumed that there is a relationship between the concentration of androgens in the body and the risk for prostate cancer. However, more than ten prospective epidemiological studies have not provided constant results yet, and only one study showed a significant relationship between the concentration of testosterone in the serum and prostate cancer.[11)] There seems to be various reasons why this controversy has not been solved. In addition to the inevitable fundamental problems of epidemiological studies, other complicated factors may also be involved, for example, a biased hormone measurement system, timing of blood collection, the levels of hormone-binding protein, individual differences in the 5α-reductase activity, etc. Furthermore, it is necessary to consider at what age the concen-

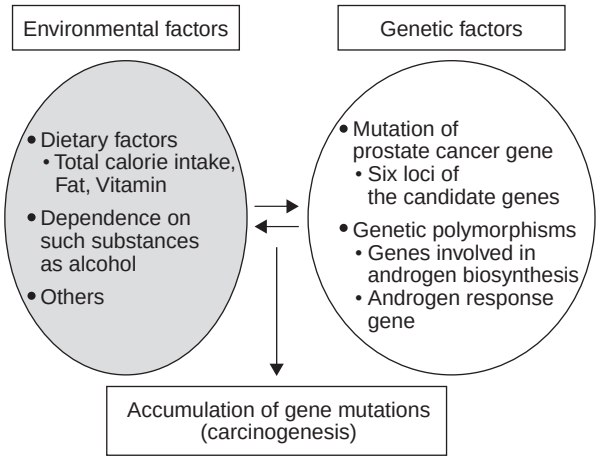

Fig. 1 Environmental and genetic factors for prostate cancer

tration of androgens has an influence on prostate carcinogenesis in human beings.

Genetic Factors for Prostate Cancer

Another definite risk factor for prostate cancer is a positive family history. Narod *et al.* reported that in a patient with a history of prostate cancer in either his brother or father, the relative risk increases 2.62 times and 1.22 times, respectively. This seems to provide evidence that a genetic predisposition plays an important role in the development of prostate cancer.

At present, it is estimated that hereditary prostate cancer, in which genetic factors play a decisive role, amounts to only 5 to 10% of all prostate cancers.[12] Up to now it has been illustrated that 6 gene loci, i.e., 1p36, 1q24-25, 1q42, 17p, 20q13, and Xq27-28 are involved, and some candidate genes have actually been identified. On the other hand, sporadic prostate cancers can develop as a result of interaction between environmental and genetic factors (Fig. 1). Concerning the genes that control the risk for the sporadic development of prostate cancers, or the host susceptibility to prostate cancer, a genetic group (*CYP 17, SRD 5 A 2, Androgen receptor gene, etc.*) involved in androgen biosynthesis and androgen response has been considered a strong candidate. Recently, a new science called molecular epidemiology has come under the spotlight, and studies on genetic polymorphisms (genetic individuality) of susceptive genes are under way at a rapid pitch.

Conclusion

Recent epidemiological studies on cancer, including environmental as well as genetic factors, have not only demonstrated the risk factors for cancers, but have also made a great contribution in illuminating the processes of carcinogenesis, enabling the identification of highly susceptive groups of carcinogens, and finally, establishing an effective strategy of preventive measures against cancer. In prostate cancer, the identification of risk factors and the promotion of active preventive medicine can provide enormous benefits to the super-aging society of our future.

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Surrogacy

JMAJ 47(4): 192–203, 2004

Shiro NOZAWA*† and Kouji BANNO**†

*President, **Deputy Secretary, Japan Society of Obstetrics and Gynecology
† Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan

Abstract: The views of the Japan Society of Obstetrics and Gynecology (JSOG) on surrogacy are outlined. The JSOG does not approve of surrogacy, either its implementation or its support, based upon the principles that: the well-being of the unborn child should be given highest priority; surrogacy is accompanied by both physical risk and mental burden; surrogacy contributes to complicated family relationships; and surrogacy contracts are not viewed as ethical by society. Surrogacy is similarly not recognized by other professional societies including the Japanese Society of Fertility and Sterility, the Japan Federation of Bar Associations, and the National Institute for Research Advancement. Very few foreign countries approve surrogacy. The United States and Great Britain, two countries that approve surrogacy, have encountered a variety of legal and ethical problems surrounding surrogacy-related issues. Thus strict bioethical foundations—based upon legal, ethical and medical guidelines—need to be established for assisted reproductive technologies because these medical procedures, including surrogacy, involve the creation of a new life with separate character and human rights. The JSOG will continue to review and amend its views on surrogacy based upon changing public consensus and social perspectives.

Key words: Surrogacy; Assisted reproductive technology; Bioethics; Japan Society of Obstetrics and Gynecology

Introduction

Following Japan's first reported case of surrogacy in May 2001, the Japan Society of Obstetrics and Gynecology (JSOG) published a draft policy statement based on a two-year review entitled "JSOG Viewpoints on Surrogacy"; this was approved by a special board meeting held on April 12, 2003 and was formally adopted by the 55th JSOG General Assembly. During this period, discussions were held based on a report submitted by the JSOG Ethics Committee (chairperson: Shiro Nozawa), a draft statement was prepared by the committee, the views of JSOG members and other relevant academic societies were compiled, and a final draft revision was carefully reviewed and approved by the Board of Directors according to formal procedures. Concurrently, the Health Sciences Council of

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 130, No. 10, 2003, pages 1463–1473).

the Ministry of Health, Labor and Welfare held formal discussions on the same issues with its committee of experts and members of the assisted reproductive technology section during this period. Thus these viewpoints of the JSOG reflect the expert opinions of a society of professionals.

The aim of this paper is to elucidate the viewpoints of the JSOG as well as the views of the national government and other relevant professional organizations and also to introduce guidelines that have been adopted in other countries. This paper should serve as a point of reference in understanding the viewpoints of the JSOG towards surrogacy.

Definition of Surrogacy

Presently, there are two types of surrogacy in actual clinical practice. One method transplants the fertilized egg of an infertile couple into the uterus of a third party female (host mother). A second method artificially inseminates the egg of a third party female (surrogate mother) using the sperm of the client husband. In the majority of overseas cases, the former is the mainstream method; this method is referred to as surrogacy or *in vitro* fertilization (IVF) surrogacy. Based on previous survey findings, this method is more socially accepted in Japan; but similar to other countries, many ethical, legal, social, and medical problems remain with regard to the unborn child, the client couple, the host mother and the families of the host mother. However, it is the opinion of a segment of the JSOG membership that if surrogacy is the only method available for infertile couples who desire to have a child, it should be recognized under certain presanctioned conditions.

Background History of the JSOG Statement[1,2)]

Laws and guidelines that regulate assisted reproductive technology do not exist in Japan. JSOG physicians practice assisted reproductive technology for married couples according to criteria established by the JSOG. However, public concern has risen concerning the merits and demerits of surrogacy following the advent of Japan's first surrogacy case in May 2001 and mediation by overseas surrogacy organizations.

Thus, in view of the rising public concern and the many existing inherent problems, the JSOG Ethics Committee (chairperson: Shohei Yonemoto) deliberated the merits and demerits of surrogacy in May 2001. The nine-member committee, consisting of six non-member experts (an ethics scholar, a member of the clergy, a legal expert, a lawyer, a pediatrician, and a journalist) conducted five committee meetings starting August 17, 2001 and submitted its committee report entitled "Ethics Committee Review — Opinions on Surrogacy" on December 12, 2001.

Based on a review of this report, the draft statement, "Views of the Ethics Committee on Surrogacy", was compiled and publicly announced in February 2002. This statement was published in the JSOG Journal (Vol. 54, No. 4) and the JSOG website, and the opinions of JSOG members and relevant societies were solicited for a three-month period until June 30, 2002. Widespread and diverse input of opinions led the ethics committee to hold further discussions to revise and clarify section 4) of the statement on surrogacy to read from "surrogacy contracts conflict with public morals" to "surrogacy contracts are not ethically approved by all sectors of society". In addition, item 2) of the future considerations list was also revised to read "a segment of the JSOG membership supports the move to recognize surrogacy", based on the diverse viewpoints regarding the merits and demerits of surrogacy that currently exist. Furthermore, the views of the JSOG statement were reported at a liaison meeting with other affiliated societies (November 26, 2002). These efforts consequently led to a complete support by the Japan Association of Obstetricians & Gynecologists and the Japa-

nese Urological Association.

The final draft statement on "JSOG Viewpoints on Surrogacy" was approved by the tenth Executive Board meeting held on March 10, 2003, was reviewed by a special board meeting on April 12, and was formally adopted by the 55th JSOG General Assembly meeting.

JSOG's Views on the Merits and Demerits of Surrogacy[3)]

Based on careful deliberations, the JSOG Ethics Committee concluded that surrogacy could not be recognized for the following four reasons. In addition, any acts that mediate, implement, or assisted surrogacy were also prohibited.

1) The well-being of the unborn child should be given highest priority.
2) Surrogacy is accompanied by both physical risk and mental burden.
3) Surrogacy contributes to complicated family relationships.
4) Surrogacy contracts are not ethically approved by all sectors of society.

These four reasons are explained in detail below.

Public Views on Surrogacy[4)]

There are no laws that regulate assisted reproductive medicine in Japan. Artificial insemination and *in vitro* fertilization for married couples have been carried out according to voluntary limitations adhered to by JSOG physicians. But recently, cases of JSOG physicians engaging in assisted reproductive technology that clearly contradict JSOG principles have emerged. Additionally, a recent court verdict supported the husband's right to deny the legitimacy of a child born through artificial insemination using donor semen (AID) conducted without the husband's consent; this verdict highlights the problem surrounding the welfare of children born through assisted reproductive technology. The advent of commercial enterprises that engage in surrogacy mediation services also reflects the diversity of the problems that stem from assisted reproductive technology. Subsequently, there is growing public need to arrive at a consensus concerning creation of a system that will be able to cope with related issues, including surrogacy, and implementation of appropriate measures.

In view of these circumstances, a committee of experts was created under the auspices of the Health Sciences Council, Evaluation Section for Advanced Medical Care, and assisted reproductive technology was intensively analyzed from a diverse professional standpoint. Discussions on surrogacy, the use of donated sperm, egg cell, and embryo were carefully conducted at a total of 29 meetings over a period of two years and two months. In December 2000, the committee prepared a statement on assisted reproductive technology using donated sperm, egg cell, and embryo.

The committee reached a consensus on the following six basic concepts.

1) The well-being of the unborn child will be given highest priority.
2) Humans should not be treated solely as a means of reproduction.
3) Safety must be adequately considered.
4) The concept of eugenics will not be allowed.
5) Commercialism will not be allowed.
6) Human dignity will be protected.

Based on these basic concepts, surrogacy (both surrogate and host mothers) was prohibited. The conclusion of the committee was based on the reasoning that surrogacy utilized the physical body of a third party as a means of pregnancy and delivery, and it directly violated the basic concept that people must not be treated solely as a means of reproduction. Moreover, the considerable risk caused by pregnancy and delivery, as well as the possible risk to the life of the surrogate mother for the approximately nine months of pregnancy also violated the concept that "safety must be adequately considered". Therefore, surrogacy could not be approved based on these view-

points. Furthermore, custody disputes between the client couple and surrogate mother were also foreseen due to the possibility of a surrogate mother developing maternal ties to the unborn child. In reality, such cases have occurred in the United States where surrogacy is recognized. Thus, it was concluded that surrogacy should be prohibited as it does not place the highest priority on the well-being of the unborn child. Additionally, the report recommends that implementation or mediation of these assisted reproductive technologies be regulated by law in conjunction with legal punitive provisions.

The section of the Health Sciences Council on assisted reproductive technology was created on June 11, 2001 based on this committee report to study specific system improvements; and the council has held a total of 27 meetings to date. Based on these discussions, the Council compiled its final draft report on "Improvements to the Assisted Reproductive Medical System Using Sperm, Egg, and Embryo" on April 10, 2003.

Viewpoints of Other Professional Organizations on Surrogacy

The issue of surrogacy has also been deliberated by other professional organizations in other sectors of society. The majority of these organizations also agree that surrogacy cannot be recognized due to the numerous problems that exist.

1. Japanese Society of Fertility and Sterility[5)]

The Japanese Society of Fertility and Sterility addressed the issue of surrogacy as early as 1992 when it conducted a questionnaire of infertile couples, its board of directors and its society members about this issue. Seventy percent of the respondents opposed surrogate mothers while approximately 45 percent supported host mothers. In 1994, the society's board members announced its views on the issue of surrogate mothers and reported that due to the social, ethical, and legal complexities surrounding surrogacy, the society was unable to reach a clear conclusion on its implementation. The following four reasons were given in support of this conclusion.

1) A disparity exists between social and ethical indications and medical indications.
2) Discussions have been inadequate concerning the medical risks for the host mother that accompany the insemination, pregnancy, and delivery process as well as the inherent social and psychological problems that exist since surrogacy centers on processes surrounding a child born outside of a marital relationship.
3) Legal solutions would be difficult to achieve.
4) Unsolved problems remain concerning monetary exchange or mediation by third parties in surrogacy.

It was further noted that there is a need to obtain a social consensus concerning these issues.

2. Japan Federation of Bar Associations (JFBA)[6)]

The Japan Federation of Bar Associations has repeatedly discussed the legal conflicts surrounding assisted reproductive technology; these issues include the various adverse effects that would stem from a continued neglect of these issues in a country where statutory regulations on assisted reproductive technologies (ART) do not exist. To prevent the abuse of and to protect human rights, the JFBA announced its proposal on legal regulations concerning the use of assisted reproductive technology in March 2003.

In this proposal, the JFBA advocates banning both surrogate and host mothers (proposal 11). This conclusion was based on concerns that a surrogate mother would be the biological mother and that the host mother would be perceived as an expedient "means of borrowing a uterus"; for both women involved in this birth process, there are overwhelming physical and mental long-term effects. In addition, it

was feared that there would be a violation of women's rights in addition to commercial exploitation.

3. National Institute for Research Advancement (NIRA)[7]

The National Institute for Research Advancement was founded by 145 key individuals from the industrial, academic, and labor sectors in accordance with the National Institute for Research Advancement Act. It is an independent, government-approved policy research institute. Its objectives are to conduct independent research of the highest quality which will contribute to the resolution of various complex issues facing contemporary society.

In its legal draft proposal on bioethics entitled "Developments in the Life Sciences and the Law", Clause 14, the NIRA announced its views to ban surrogacy contracts that approve of delivery and birth of children from third-party women.

Public Consensus on Surrogacy

What is the public consensus about surrogacy in Japan?

Based on our findings, a number of diverse surveys has been conducted on various segments of society since 1990.

1. Survey conducted by Yasuko Shirai (1990)[8,9]

The findings of Yasuko Shirai's survey conducted in 1990 are described in the "Bioethics on the Birth of Life" by Kiyoko Kinjo (published by Nippon-Hyoron-Sha, Co., Ltd.). This survey showed that only 4.4 percent of both men and women supported surrogate mothers and only 4.7 percent supported host mothers.

2. Questionnaire survey conducted by the Japanese Society of Fertility and Sterility (1992)[10]

A survey conducted by the Japanese Society of Fertility and Sterility of its board of directors and society members showed an approval rate of 11.6 percent for surrogate mothers and a 40.4 percent approval rate for host mothers. Moreover, the approval rate for the use of surrogate mothers by couples undergoing infertility treatment was approximately 16 percent, while the approval rate for host mothers was 43.3 percent among husbands and 49 percent among wives of infertile couples.

3. Survey conducted by the Japan Public Opinion Poll Association (1996)[9]

"Bioethics on the Birth of Life", by Kiyoko Kinjo (published by Nippon-Hyoron-Sha, Co., Ltd.) reports the public survey findings of the Japan Public Opinion Poll Association in 1996 with regard to the question, "what is your opinion about surrogate mothers". The survey showed that 8.7 percent of the respondents replied that "they would use surrogacy if no other fertility options were available", 29.8 percent responded that "they would not use surrogacy, but were not opposed to other couples using surrogacy", and 56.3 percent stated that "they were opposed to the use of surrogacy because the child produced was not the biological child of the couple". If the first two responses are interpreted as an affirmative response, the approval rate is 38.5 percent and the non-approval rate is 56.3 percent.

4. Questionnaire survey on ART by Takumi Yanaihara, Chief Researcher, Health Sciences Council Special Research Group[11]

The 1999 questionnaire survey on ART conducted by Takumi Yanaihara, chief researcher, Health Sciences Council Special Research Group, had a total of 6,006 respondents of which 4,000 were members of the general public. This was Japan's first significant and large-scale survey on assisted reproductive technology.

With regard to the approval of surrogacy, 7.0 percent responded that surrogate mothers "should be recognized", 36.7 percent responded that "surrogate mothers should be recognized

under certain conditions", and 37.4 percent responded that "surrogate mothers should not be recognized". Concerning host mothers, 9.2 percent responded that "host mothers should be recognized", 43.6 percent responded that "host mothers should be recognized under certain conditions", and 29.7 percent responded that "host mothers should not be recognized". Among physicians at registered *in vitro* fertilization facilities, other obstetricians/gynecologists, and pediatricians, the majority opposed recognizing surrogate and host mothers; this rate was higher than that of the general public. The rate of disapproval for host mothers by these physician groups was 41.0 percent, 42.5 percent, and 47.3 percent, respectively.

In addition, with regard to actual use of surrogacy and host mothers, 82.4 percent and 68.8 percent of the general public responded that "they would not utilize surrogate mothers even if their spouse requested it". Among infertility patients, 84.7 percent and 70.3 percent responded, "they would not utilize host mothers even if their spouse requested it". Thus, the results indicate that the demand for surrogacy among the general public and infertility patients is not very high.

5. Questionnaire survey on ART by Zentaro Yamagata, Chief Researcher, Health Sciences Council Special Research Group (2003)[12)]

A questionnaire survey on 5,846 randomly chosen subjects in 200 locations throughout Japan was conducted in 2003. As a result, the approval/disapproval rate of the general public for surrogacy showed that about 33 percent disapproved of surrogate mothers, which exceeded the 30 percent of respondents who approved of surrogate mothers. Approximately 40 percent of the respondents approved of host mothers, but the approval rate did not exceed 50 percent. In addition, more than 30 percent responded as "did not know" and this rate also did not exceed 50 percent. Overall, among the respondents who stated that they would recognize surrogacy, 30 percent responded that "they would approve of surrogate mothers under certain conditions" and 34.2 percent responded that "they would not approve of surrogate mothers". Concerning host mothers, 44.3 percent responded that "they would approve of host mothers under certain conditions" and 23.9 percent said that "they would not approve of host mothers".

The results of this survey suggest that there is a tendency to tolerate host mothers rather than surrogate mothers; however, compared to the findings of the 1999 questionnaire survey on ART (conducted by Takumi Yanaihara, chief researcher, Health Sciences Council Special Research Group) there is a decrease in the approval rate towards both surrogate and host mothers (an approximately 47 percent approval rate for surrogate mothers in the Yanaihara survey, an approximately 30 percent approval rate in the Yamagata survey; similarly, an approximately 53 percent approval rate for host mothers in the Yanaihara survey and an approximately 44 percent approval rate in the Yamagata survey), although it must be kept in mind that different questions were used and the target population differed.

Among the general public that replied that "they would not use surrogate and host mothers even if requested by their spouse", the response rate was 76.2 percent for use of surrogate mothers and 58.7 percent for use of host mothers. Thus the majority of the general public responded that they would not utilize either surrogate or host mothers even if their spouse desired it.

Based on these findings, it can be concluded that there is no evidence that supports a general public trend towards the acceptance of surrogacy over the last few years.

Situation in Other Countries

1. The merits and demerits of surrogacy in other countries[13)]

Is surrogacy widely practiced in other coun-

tries throughout the world?

According to the findings of the International Federation of Fertility Society Surveillance (IFFS) survey in 1999 on IVF surrogacy in 37 countries, IVF surrogacy was practiced in only 15 countries. The majority of the countries surveyed had banned the practice. Thus, the perception that surrogacy is widely practiced worldwide is erroneous.

2. Surrogacy in the United States

The United States is the most representative example among advanced nations where surrogacy is practiced, but it is not allowed in all states.

According to the findings of the Health Sciences Council Special Research Group (chief researcher: Shinya Matsuda) on the present status of assisted reproductive technology using donated ovum, sperm, and embryo, there were only 11 states that had statutory laws recognizing surrogacy contracts (Alabama, Arkansas, Florida, Illinois, Iowa, Nevada, New Hampshire, Tennessee, Virginia, West Virginia, and Wisconsin), while 11 states did not recognize the legality of surrogacy contracts (Arizona, Washington D.C., Utah, Indiana, Kentucky, Louisiana, Michigan, Nebraska, New York, North Dakota, and Washington). Many of the latter states have banned surrogacy contracts due to conflicting public policy; while the invalidity of surrogacy contracts is not necessarily enforced, monetary remuneration is prohibited. Violations are punishable by civil law or criminal charges.[14)]

Although surrogacy is recognized in some states, a variety of problems stemming from surrogacy have emerged. This is exemplified by the famous Baby M case of New Jersey in 1986 described in Masahiko Hiroi's report.[15)] The surrogate mother of Baby M refused to relinquish the infant after birth. Although the Family Court recognized the surrogacy contract, the Supreme Court annulled its validity. The Court decision was based on the reasoning that the surrogate mother's dignity had been damaged and further ruled that the transfer of money to adopt a child was illegal. The infant was placed in the custody of the client in the best interests of the child's welfare and the surrogate mother was given free visiting rights. In 1990, a surrogate mother who gave birth through a donated embryo filed suit for exclusive parental rights; however the courts did not recognize her parental rights and she was denied the right to see or visit the infant. These two cases exemplify the disputes that may occur between the clients and a surrogate mother over the infant. In addition, there have been cases where the unborn child was discovered to be physically handicapped or had been infected with HIV through an HIV-positive surrogate mother and disputes between the clients and the surrogate mothers over the refusal to claim the infant have also occurred. In 1995, a 26-year old single male in Pennsylvania, who claimed the child of a surrogate mother, killed the five-week old infant in anger when it cried all night. Yasunori Yoshimura reports that there have been more than 40 cases of surrogacy-related court disputes over the adoption of the unborn infant,[16)] and the perception that surrogacy in the United States is free of controversy is inaccurate.

Tadahiro Fujikawa reports in "Policy Research — Developments in the Life Sciences and the Law"[7)] that Dr. LeRoy Walters, Director of the Joseph P. and Rose F. Kennedy Institute of Ethics at Georgetown University suggests that surrogate mothers tend to come from economically poor backgrounds and are, in essence, selling children. Thus, surrogacy conflicts with public policy. In addition, when the surrogate mother was the sister of the client, it was pointed out that if the client mother were to eventually tell the child that "she was not his/her natural mother", the surrogate-client relationship between family members may prove more difficult than in the case of a commercially-contracted surrogate mother.

The American College of Obstetricians and

Gynecologists (ACOG) ethics guidelines on surrogacy[17] report that only a few states have approved of the surrogate mother system but only in cases where certain conditions have been met.[18] The guidelines recognize that proper informed consent is necessary for surrogate mother cases as it is possible to release the child after birth, when there is the possibility that the risk to the child's well-being is greater than any advantages that may be gained. The guidelines also recognize that diverse opinions on surrogacy exist and that physicians may oppose surrogacy. The guidelines also delineate the ethical responsibilities of obstetricians and gynecologists who participate in the surrogate mother system at various levels. In addition, preventive measures that should be taken to avoid medical, psychological, and legal damage to the client couple, surrogate mother, and the unborn child are also described. It should be noted that in Japan, mental health counseling services and other support systems do not exist. Moreover, the ACOG guidelines clearly state that physicians have the legitimate right to refuse participation in the surrogacy process for either ethical or medical reasons.

3. Surrogacy in Europe

According to the findings of the "Study on the System and Conditions Related to Assisted Reproductive Technology Utilizing Donated Ovum, Sperm, Embryos in Other Countries" conducted by the Health Sciences Council Special Research Group (chief researcher: Shinya Matsuda), the advanced European countries of France, Germany, and Sweden do not recognize surrogacy. In France, civil law states that surrogacy contracts, in which surrogate mothers give birth to an infant and then yield all mother-child rights to another woman, are invalid. In Germany, surrogacy is legally banned under its anti-mediation law. Mediators are punishable by an imprisonment of less than one year or by fines and penalties, those who gain monetary profit are punishable by an imprisonment of less than two years, while those who engage in surrogacy as a commercial enterprise are punishable by an imprisonment of less than three years.

In contrast, Great Britain is one of the countries in which surrogacy is recognized. Nonprofit surrogacy mediation services, surrogacy contracts, and involvement in these processes are not considered illegal. However, Michiko Ishii's paper, "Policy Research — Developments in the Life Sciences and the Law",[7] reports that the Ministry of Health in Great Britain has prepared guidelines on the remuneration and costs related to surrogacy, which is seen as a last-resort measure for infertile couples. The historical context of the current 1985 law on childbirths is based on the public antipathy toward third parties who utilized surrogate mothers for profit-making motives. An awareness of the legal and ethical problems surrounding surrogate mothers exists and the British government has attempted to control the practice as much as possible.

These circumstances reflect the fact that there is a shared awareness of the many problems inherent to surrogacy in both Great Britain and the United States, two nations in which surrogacy is practiced.

Why the JSOG Does Not Recognize Surrogacy

The ACOG guidelines state that studies that assess the damages and profits related to surrogacy are limited.[17,19,20] The inadequacy of such data, even in the few states in the United States where surrogacy is recognized, has been pointed out, as well as the need to conduct such research. In view of these circumstances, the evidence necessary to assess the socio-ethical problems associated with surrogacy is inadequate. However, based on a diverse evaluation of the problems inherent to surrogacy as medical treatment, the JSOG has decided not to recognize surrogacy based on the following four reasons.

1. The well-being of the unborn child should be of highest priority.

In reviewing assisted reproductive technology, including surrogacy, society in general as well as the physician and the patient place the greatest emphasis on the happiness and well-being of the conceived child. The same views are supported in the research of Yuri Aono and Tomoko Sakota.[21,22] The MHLW Health Sciences Council Special Committee report also supports the idea that "the well-being of the unborn child takes precedence over all other issues". In a special "Reproductive Biology" issue of Science, Dr. Peter Braude discusses the importance of studying these issues from the unborn child's perspective in the opening editorial,[23] which is similar to the views of the JSOG, and states that the importance of the unborn child's well-being should take precedence over the client's rights or the surrogate mother's right to self-determination. Significant priority was placed by the JSOG on this issue as it selected the phrase, "to give highest priority" to reflect the shared viewpoint of the client and surrogate mother that the unborn child's well-being took precedence over all other issues.

With respect to children's rights, the Convention on the Rights of the Child (adopted by the U.N. General Assembly in 1989) states that "parties shall take all appropriate national, bilateral and multilateral measures to prevent the abduction of, the sale of or traffic in children for any purpose or in any form" (Article 35). In surrogacy, the surrogate mother is contracted to bear the burden of pregnancy and to give birth, yet she relinquishes the child to the client. This act in itself ignores the mother-child ties that are created through pregnancy and birth and is considered to violate the child's well-being. In addition, according to Kayoko Saito's paper, surrogacy violates Clauses 3, 8, 9, and 21 as well as Clause 35 of the Convention on the Rights of the Child (adopted by the U.N. General Assembly in 1989).[24] This is especially true if the one of the two parties does not abide by the surrogacy agreement, i.e., the surrogate mother refuses to hand over custody of the child or the client refuses to accept custody of the child as the child does not meet the client's expectations. In the United States, more than 40 such court cases have been reported. In these situations, not only do the child's living conditions become notably unstable, but the child's formation of proprioception and self-identity as well as emotional development are hindered. Therefore, in these regards surrogacy is not recognized due to the deep emotional suffering foreseen for the child.

2. Physical risk and mental burden accompany surrogacy.

Physical risk accompanies pregnancy and the birth process — this is an undeniable fact. The medical risks that exist for the surrogate mother have been clearly stated in the ACOG guidelines for surrogate mothers, in the Japanese Society of Fertility and Sterility's "Views on Surrogacy", as well as by the JSOG. In surrogacy, the physical and mental burden that accompany pregnancy and birth are forced on a third party female who is essentially unrelated to the pregnancy and birth; this situation undermines human dignity. Kenichi Tatsumi summarizes these problems.[25] Irrespective of whether a surrogacy contract is based on a thorough explanation and agreement of its content by the parties involved, there is the risk that the surrogate mother may experience unanticipated psychological hardship and emotional distress. Thus, surrogacy exceeds the limits of allowable fertility treatment.

3. Family relationships become complex.

Throughout the world, it is generally regarded that the woman who becomes pregnant and gives birth is that child's mother. In Japan, this fact is also legally recognized according to the Supreme Court ruling (civil law April 27, 1962, Volume 16, No. 7, page 1247) and substantive enactment to that effect is expected in the near future. At that time, it is anticipated that

surrogacy contracts will add to the complexity of family relationships and become a source of needless friction and confusion to social order.

There is the viewpoint that due to the rising divorce rate in Japan, family relationships have already become diversified and complex. Meanwhile, there is the opinion that parent-child ties are formed throughout the pregnancy and birth process. Mitsuhiro Sugimoto states that,[26] "the biological mother", "the birth mother", "the custodial mother", and "the legal mother" are undesirable examples of the complex parent-child ties that are created by surrogacy. He points out that in Japan, the well-being of the child may be sacrificed in surrogacy due to the complex parent-child ties that exist prior to the child's birth. Social conventions and laws, which ensure that the complex parent-child ties created by surrogacy do not hinder the unborn child's well-being, are necessary; but in present-day Japan, such legal or social guarantees do not exist. Therefore, surrogacy cannot be sanctioned.

4. Society does not ethically sanction surrogacy contracts.

The surrogacy contract commercializes the maternal body for financial compensation and recognizes the trade in children, which places the surrogate mother in physical and mental subjugation. Even without financial compensation, society still view surrogacy contracts as violations of public order and morality (Civil Law, Article 90).[9,27–29] "Public order and morality" is a legal term, which is generally unfamiliar and susceptible to misunderstanding, so the wording was revised to "society does not ethically sanction surrogacy contracts". For surrogacy contracts to be accepted, the general consensus of society must not oppose this argument. Presently, these conditions do not exist, and likewise surrogacy contracts cannot be recognized.

If this position is further neglected, third parties who provide for profit surrogacy mediation services will appear to economically exploit vulnerable women, consequently triggering a trade in children; thus, surrogacy mediation was also prohibited.

5. Other issues

(1) Importance of voluntary compliance to JSOG's ethics ruling

As a professional organization, the JSOG strongly hopes that each member will abide by its ethical guidelines, and recognize that irrespective of the legal debates, the diverse and inherent ethical, legal, and medical problems posed by surrogacy affect not only the client couple, but also the unborn child, surrogate mother, and their respective families, in addition to society as a whole.

(2) Future issues

The JSOG concluded that it would not recognize surrogacy. However, it recognizes that there are those members who would sanction the practice of surrogacy under specified conditions (e.g., based on third-party reviews, legal revisions that define parent-child relationships, etc.), if surrogacy is the only means of conceiving a child. It also recognizes that as social perspectives change, tolerance for surrogacy may also rise. Thus, it is important that the recognition of medical practices such as surrogacy is based on consensus of society as a whole. If such a consensus were to be realized, the collective opinion of the JSOG would be to review the issues as required in only exceptional cases in which it would be detrimental to unilaterally prohibit surrogacy from a medical standpoint.

It was also concluded that such a review must be based on an awareness that surrogacy may deviate from orthodox social perspectives concerning parent, child and family relationships traditionally held in Japan. In addition, the well-being of the unborn child must be adequately protected. Thus, various measures, including the creation of an investigative body, must be undertaken prior to recognizing a limited number of surrogacy cases.

Reproductive Rights and the Right to Self-Determination

Among the viewpoints that support the recognition of surrogacy, are those views that support the reproductive rights of infertility patients and their right to pursue happiness, as well as the patient and surrogate mother's right to self-determination. The most representative of these viewpoints are those of Kazumasa Hoshino and Kiyoko Kinjo. But there are also many academic scholars who oppose these views. In his book, "Reproductive Revolution and the Law", Tadahiro Fujikawa (published by Nihon Keizai Hyoron Sha) states that Noriko Mizuno questioned "whether reproductive rights should be called rights"; these issues were discussed at the symposium on life ethics draft laws held in March 2001.[30] Akiko Nagaoki states that reproductive rights and the right to self-determination are terminology that originated from a woman's resistance to third-party interventions of her reproductive functions and her physical body. These terms were used to question a society that would allow third-party intervention of individuals. She points out that the terminology did not denote the freedom to do whatever an individual desires with regard to her physical body. Masayoshi Tarui states that a woman's right to utilize ART should not be taken in the same context as social rights such as the right to education and health care.[31]

The JFBA's "proposal on legal restrictions on the use of ART" states that although reproductive rights is one aspect of the right to self-determination, the JFBA standpoint is that restrictions exist with regard to reproductive rights because it directly concerns the unborn child conceived through ART, including surrogacy.

Among the various authors mentioned above, Tadahiro Fujikawa's opinion is that in view of the unborn child, the reproductive rights of a parent should be restricted. Similarly, Naoko Kakee also believes that the creation of a new life or a separate individual through reproductive assistance technology, exceeds the limits of an individual's right to self-determination.[32] In addition, there are those who advocate the surrogate mother's right to self-determination. However, there are also opposing viewpoints. Takao Yamada states that the right to self-determination of a childbirth-substitute such as a surrogate or host mother cannot be supported.[33] The underlying reason is that the right to self-determination is appropriate only when such rights do not go against the interest of others. Surrogacy greatly affects the client and their families as well as the unborn child.

Conclusion

The historical background and content of JSOG's "Views on Surrogacy" have been examined in this paper. The greatest issue that must be addressed with regard to assisted reproductive technology as well as surrogacy is that this process differs from other types of medical transplantation as it involves the creation of a child with a separate character and human rights. Therefore, surrogacy is not an issue that can be decided solely on agreements between physicians and patients, but requires the consensus of the general public as well as a social order that protects the unborn child.

The JSOG will continue to observe the gradual changes in public consensus and social perspectives; and if society heads in the direction of recognizing surrogacy, the JSOG will review its viewpoints as required. It is hoped that this paper will help further the understanding of JSOG's viewpoints on this issue.

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