INTRODUCTION

Since the birth of Louise Brown, the first IVF baby in 1978, currently, more than 1.7 million cycles of assisted reproductive technology (ART) are carried out annually worldwide, and more than 400,000 children are born by ART although the data for some countries and regions are not included. ART is widely used as a standard infertility treatment. However, the major difference between reproductive medicine and other medical care is that reproductive medicine is related to the birth of the next generation. Although ART has been performed safely, there are several genetic challenges. It is appropriate to provide genetic information prior to the start of ART, and specific counseling is required for patients with or likely to have genetic changes.

Genetic counseling is a medical practice that provides and supports appropriate genetic information for patients/family.
members of hereditary diseases or those who have the possibility to be able to decide and act on life plan choices by themselves. In genetic counseling, it is performed step by step, such as whether it is a chromosome issue or a gene issue. In addition to genetic counseling in infertility treatment, it is important to clarify whether it is the cause of infertility, whether it is related to infertility treatment, or whether it may affect the born child or not. For genetic counseling in reproductive medicine, it is appropriate to respond before starting ART.

Common genetic counseling is often initiated from a disease, whereas in genetic counseling in reproductive medicine, healthy couples often undergo genetic testing as an infertility screening test. Genetic change is recognized, and they will see counseling. Compared to the frequency of genetic disorders in female infertile patients who experience menstruation, the rate of genetic disorders is high in male infertility.

Regarding the association between ART pregnancy and congenital defects in ART, though there is no statistically significant difference between ART and natural conception. It has been clarified that the birthweight of a baby born by fresh embryo transfer is lighter than that of a naturally pregnant baby. On the other hand, babies born by frozen-thawed embryo transfer are heavier than babies born by natural conception.

Imudia et al reported that serum E2 > 3,450 pg/ml significantly increased the risk (OR: 9.40, 95% CI: 3.22-27.46) of low birthweight infants in 292 singleton pregnancies by fresh embryo transfer. Pereira et al analyzed 4071 singleton pregnancies by fresh embryo transfer and reported that serum E2 > 2500 pg/ml was an independent risk factor (OR: 10.8, 95% CI: 9.2-12.5) for the birth of low birthweight infants. High estrogen levels during fresh embryo transfer are thought to be responsible for low birthweight.

It has been reported that the incidence of hypertensive disorder of pregnancy (HDP) is increased in pregnancy by frozen embryo transfer. According to an analysis based on Japan's 2014 ART database, gestational hypertension nephropathy was 1.43 times (95% CI: 1.14-1.80) and placenta accreta was 6.91 times (95% CI: 2.87-16.66) in frozen embryo transfer under the hormone replacement cycle compared with the natural cycle. It has been reported that the corpus luteum–derived factor does not work under the hormone replacement cycle, and it becomes poorly adapted to changes in hemodynamics associated with pregnancy, which may increase the incidence of preeclampsia.

It has been pointed out that placenta previa, residual placenta, and postpartum bleeding increase in pregnancy by in vitro fertilization. Smoking, endometriosis, and endometrial thickness are cited as independent placenta previa risks, and endometrial thickness at transplant is 2.02 times (95% CI: 1.12-3.65, P = .02) at 9-11 mm compared with less than 9 mm, 3.74 times (95% CI: 1.90-7.34, P < .01) for 12 mm or more, and it has been reported that the incidence of placenta previa increases. The thickness of the endometrium at the time of transplant is related to the risk of placenta previa, and it is considered important to adjust the endometrium to obtain an appropriate endometrial thickness.

The association between ART and complications includes various confounding factors such as the background of spermatogenic disorders, ovulation affects, aging, and district have an effect. There is also increasing evidence that infertility is an independent risk factor for obstetric complications and perinatal adverse outcomes without the addition of ART. Therefore, technique-related risks cannot be independently eliminated. ART is a safe alternative for couples who are otherwise unable to conceive, but the risk requires thorough evaluation and counseling before ART is performed.
3 | CHROMOSOMAL ABNORMALITIES

The frequency of chromosome abnormalities in the general population is approximately 0.65% in screening tests for newborns, and chromosomal abnormalities in infertile patients are 0.595% in women and 0.64% in men.9-11 Especially for couples who are treated with ART, the incidences of chromosomal abnormalities are 1.2%-2.1% in female and 1.1%-6.1% in male.1,9-12 In addition, it is observed in 3.8%-18.4% in severe oligospermia and 14.7%-35% in azoospermia.13,14 (Table 1).1,9-14,41 Chromosomal abnormalities include aneuploidy and structural abnormalities.

3.1 | Aneuploidy

Aneuploidy is an abnormality in the number of chromosomes with a large or small number of chromosomes, and the mechanism due to meiotic nondisjunction. Patients undergoing infertility treatment are adults of sexual maturity, and it is necessary to consider separately the chromosomal abnormalities that are taken up as problems of the patient themselves and the chromosomal abnormalities that are taken up as problems of the resulting embryos, fetuses, and neonates. Aneuploidy includes autosomal aberrations and sex chromosome aberrations. Sex chromosomal aneuploidy is the most common abnormality among human aneuploidy, especially in infertile male patients.

Klinefelter’s syndrome (KS) is the most frequent observed sex chromosomal abnormality, with an estimated frequency of 1:500 to 1:1000 men.11,42 KS has an extra X chromosome (genotype XXXY) instead of the usual male sex complement (genotype XY). The classic form of KS, which is present in the 80%-90% of the cases, is defined by a 47,XXXY karyotype resulting from the aneuploidy of the sex chromosomes, whereas higher-grade aneuploidies (eg, 48, XXXY or 48, XXXYY), structurally abnormal X chromosome (eg, 47, iXqY), or mosaicisms (eg, 47,XXXY/46,XY) make up approximately in the remaining 10%-20% of cases.43 For any genotype, hypogonadism is a common symptom in KS.43 The prevalence of KS rises to 3%-4% among infertile males and 10%-12% in non-obstructive azoospermia (NOA).11 This may indicate that the rise of the KS might be related to the parental meiotic alterations. The recurrence rate is low due to chromosomal inactivation during gametogenesis. KS patients have a phenotype, which is extremely variable,43-47 but without any obvious facial dysmorphology that makes them indistinguishable from the boys with normal karyotype.45 It is rarely diagnosed in childhood and adolescence and is often diagnosed by infertility examination. The mean age of diagnosis is in the mid-30s reproductive age.42 Because spermatogenesis has affected in KS, surgical correction for spermatozoa is required frequently. It has been reported that many KS patients could conceive a child with TESE (testicular sperm extraction)/ICSI, and the offspring were healthy with normal karyotypes.48-50 The risk of ART for patients with KS is not high.51 Sperm retrieval rates (SRRs) in KS adults are approximately 50%-70% with TESE and micro-TESE, which are higher than those of other NOA cases.49,52,53 However, the SRR in KS patients decreases with aging.49,52,54 In the exception of sex chromosome abnormalities in men, there is 47,XYY syndrome, which has an incidence of 0.1% of male births.18

Turner syndrome (TS) is one of the most common sex chromosomal abnormalities in women. Turner syndrome is a monosomy of the X chromosome, typically 45,X, and includes structural abnormalities such as i(Xq), Xp-, Yp-, and various mosaics. Although it is a disease with a high miscarriage rate, it is present at 0.05%-0.125% in female birth. Turner’s syndrome may be diagnosed in early childhood due to skeletal signs such as valgus elbow and fourth metacarpal shortening, soft tissue signs such as pterygium and lymphedema, visceral malformations such as aortic constriction and renal malformation, congenital lymphedema, and sensorineural hearing loss. However, it is often diagnosed as short stature or amenorrhea after puberty. In many cases, premature ovarian insufficiency (POI) has already occurred in TS, at the time of infertility treatment, because of homologous chromosome pairing failure at meiosis.55,56 The rate of spontaneous pregnancy is about 2%-5% in TS.57 It has been reported healthy offspring from TS with their own oocytes.58 Trisomy X (47,XXX genotype) is also one of the most common female

| TABLE 1 | Possibility that either couple is a chromosome carrier1,9-14,19 |
| --- | --- | --- | --- | --- | --- |
| Female (%) | Male (%) | Total | KS | Autosomal t | Rob |
| --- | --- | --- | --- | --- | --- |
| General population | 0.85 | 0.85 | 0.1-0.2 | 0.25 | 0.1 |
| Infertility | 0.595 | 0.64 | 0.5-1.0 | 0.8 | 9-11 |
| Couples in ART | 1.5 | 1.1 | 2-5 | 3.4 | 13,14 |
| Couples with ICSI | 2.1 | 6.1 | 2-5 | 3.4 | 13,14 |
| Severe oligospermia | – | 5-7 | 5-10 | |
| Azoospermia | – | 10-15 | 5-10 | |

Note: The reason that the proportion of chromosomal aberration in the general population is higher than that in infertile patients may be that those with severe clinical symptoms are not included in infertile patients.

Abbreviations: Autosomal t, autosomal translocation; KS, Klinefelter’s syndrome; Rob, Robertsonian’s translocation.
chromosomal abnormalities, occurring in approximately 0.1% of female births. The disease presents with a variable phenotype caused by the presence of an extra X chromosome. Pubertal onset and sexual development are usually normal in trisomy X; however, there have been cases of POI. Sex chromosome aneuploidy should be the most common cause of POI.

3.2 | Structural abnormalities

Chromosomal structural abnormalities include reciprocal translocation and the Robertsonian translocation. Reciprocal translocations occur when heterologous chromosomes are cleaved or rearranged. Reciprocal translocation includes balanced and unbalanced types.

An example of a breakpoint in a chromosome test is shown in the figure (Figure 1). Translocations usually occur only between two chromosomes. All-arm reciprocal translocation between homologous chromosomes is impossible to acquire a live child. The person does not affect the phenotype unless there is an overall excess or deficiency, and the carrier is healthy. So, a balanced reciprocal translocation refers to a translocation in which the gene is missing or negligible and the phenotype is normal. The frequency of reciprocal translocation is generally about 0.25%, but it is found in 0.5%-1.0% in infertile men. When an unbalanced gamete is subjected to fertilization, an embryo with an abnormal chromosome number is formed. Although there are 16 karyotypes of gametes, there are nine types that can be born. Because of the chromosomal imbalance, the meiosis of gametogenesis stops in the middle and may exhibit spermatogenic dysfunction. In fact, half of the embryos are of normal karyotype or balanced type. The proportion of chromosomal imbalance in gametes subjected to fertilization has decreased.

### Table 2: Subgroup of human chromosome

| Group | Chromosome No. | Length | Location of centromere |
|-------|----------------|--------|------------------------|
| A     | 1-3            | Long   | Metacentric chromosome or submetacentric chromosome |
| B     | 4-5            | Long   | Submetacentric chromosome |
| C     | 6-12, X        | Moderate | Submetacentric chromosome |
| D     | 13-15          | Moderate | Acrocentric chromosome |
| E     | 16-18          | Relatively short | Metacentric chromosome or submetacentric chromosome |
| F     | 19-20          | Short  | Metacentric chromosome |
| G     | 21-22, Y       | Short  | Acrocentric chromosome |

### Figure 1: Types of segregation at meiosis in reciprocal balanced translocation. Balanced translocation chromosomes can segregate 2:2 (ie, two chromosomes go to each pole) and 3:1 (ie, leading gametes with 22 or 24 chromosomes). There are three types of 2:2 segregation, described as alternate, adjacent 1, and adjacent 2. Both adjacent 1 segregation and adjacent 2 segregation yield unbalanced gametes.
most chromosomally abnormal embryos are spontaneously culled as arrested growth or implantation failure. The ratio of natural selection is due to the size of the translocation segment. Chromosomes have centromeres that lie between short arms and long arms as a boundary. Chromosomes are classified from Group A to Group G according to their size and centromere location (Table 2). The chromosomes in Group D and Group G, whose short arms are extremely short, are called acrocentric chromosomes (Figure 2).

The Robertsonian translocation is present in 0.1% of the general population and 0.8% of male infertile patients. Among them, azoospermia factor (AZF), a gene related to spermatogenesis, is present in the long arm of the Y chromosome. AZF microdeletion is observed in 2%-10% of severe oligospermic men and in 5%-15% of non-obstructive azoospermic men. AZF has been classified into three areas: a, b, and c, and AZFc deletion is a maximum frequency of 80%, and the frequency of AZFa is 0.5%-4%, 1%-5% in the AZFb region, and 1%-3% in the AZFb + c region. However, it has been revealed that there are five palindrome structures in the long arm of the Y chromosome. The palindrome structure has a homologous and co-directional set structure in its base sequence, and deletion occurs as a result of pathological recombination between sets. For example, recombination between P5 and proximal P1 results in AZFb, and recombination between P5 and distal P1 results in AZFb + c (Figure 5). In AZFa deletion, the histological phenotype is Sertoli cell-only syndrome (SCO), and in AZFb deletion, it is maturation arrest. In cases with AZFa deletion and/or AZFb deletion, the possibility of sperm recovery is unlikely even if testicular sperm extractions performed. So, AZF is used to evaluate the possibility of sperm collection. Although there are various theories in the evaluation of the AZFc region, the possibility of sperm recovery can be expected to be about 70% even in the case of trisomy.

4 | Y CHROMOSOME MICRODELETIONS

Along with chromosomal abnormalities, another genetic factor for male infertility is YCMs. Several YCMs have been reported to be involved in male infertility. Among them, azoospermia factor (AZF), a gene related to spermatogenesis, is present in the long arm of the Y chromosome. AZF microdeletion is observed in 2%-10% of severe oligospermic men and in 5%-15% of non-obstructive azoospermic men. AZF has been classified into three areas: a, b, and c, and AZFc deletion is a maximum frequency of 80%, and the frequency of AZFa is 0.5%-4%, 1%-5% in the AZFb region, and 1%-3% in the AZFb + c region. However, it has been revealed that there are five palindrome structures in the long arm of the Y chromosome. The palindrome structure has a homologous and co-directional set structure in its base sequence, and deletion occurs as a result of pathological recombination between sets. For example, recombination between P5 and proximal P1 results in AZFb, and recombination between P5 and distal P1 results in AZFb + c (Figure 5). In AZFa deletion, the histological phenotype is Sertoli cell-only syndrome (SCO), and in AZFb deletion, it is maturation arrest. In cases with AZFa deletion and/or AZFb deletion, the possibility of sperm recovery is unlikely even if testicular sperm extractions performed. So, AZF is used to evaluate the possibility of sperm collection. Although there are various theories in the evaluation of the AZFc region, the possibility of sperm recovery can be expected to be about 70% even in the case of trisomy.
of complete deletion in the AZFc region. Although a gr/gr region deletion exists in the AZFc, no significant correlation was observed between the gr/gr region deletion and spermatogenesis in the Japanese population. Although men with severe spermatogenic disorder have been able to raise their children by ICSI, if the spermatogenic disorder is due to the AZF microdeletion, and a boy is delivered by the contribution of ICSI, YCMs are inherited and similar genetic aberrations may be transmitted. In addition, microdeletions may newly occur or expand, and the range of inherited microdeletions may be expanded, resulting in a worsening of spermatogenic disorder than the father.

It is important to fully explain them before ART.

5 | POSSIBILITY OF CHROMOSOMAL ABNORMAL PREGNANCY IN OLIGOSPERMIA REQUIRING ICSI

Since 1992, the development of intracytoplasmic sperm injection (ICSI) has rejoiced couples with infertility and especially those affected by severe male factor infertility. There are two concerns about the safety of ICSI. The first is the possibility of fertilization operations affecting the embryo, and the second is an increase in birth defects due to the use of severe oligo-, astheno-, and/or teratozoospermia. The former is denied, while the latter increases some...
chromosomal abnormalities.\textsuperscript{9,20,88-90} Prenatal diagnosis of post-ICSI pregnancy has reported 2.96% of chromosomal abnormalities, 1.39% of structural abnormalities such as parental translocations, 1.58% of de novo chromosomal abnormalities, 0.63% of sex chromosomal abnormalities, 0.5% of autosomal aneuploidies, and 0.44% of structural abnormalities, which were not derived from the parent. These chromosomal abnormalities occur 3-5 times the general frequency.\textsuperscript{9} As the background of the increase in the numerical chromosomal abnormalities, aging of the wife is considered as a confounding factor. However, in advanced oligospermia and asthenozoospermia that require ICSI, the reason is the high incidence of spermatozoa with chromosomal abnormalities. The risk of congenital malformation is 7.1% for ICSI and 4.0% for the general population (OR: 1.99, 95% CI: 1.87-2.11).\textsuperscript{91} It has been reported that when sperm is damaged by oxidative stress, sperm DNA is damaged. The percentage of sperm with this damaged DNA is called the DNA fragmentation index (DFI). A high sperm DFI (over 15%) will increase the miscarriage rate.\textsuperscript{92,93}

6 | EPIGENETIC ALTERATIONS

Epigenetics is a mechanism found in mammals that changes the gene expression without changing the DNA sequence.\textsuperscript{94,95} Although in many genes, the expression control is the same regardless of whether it is derived from the father or the mother, the genome imprinting is an epigenetic phenomenon in which the expression of the gene derived from the father is different from the expression of the gene of the mother. For some genes called imprinted genes, only genes from either the father or mother are expressed, other genes are suppressed, and the genes function normally in that combination. An imprinted gene is due to inactivation by methylation. The gene to be expressed is not expressed, or the gene to be suppressed is expressed, or two chromosomes that should be received one by one from both parents are inherited from one parent only (uniparental disomy), imprint gene on / off does not go well, and disease develops. It has been reported imprint abnormalities, such as Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome, Silver-Russell syndrome, and retinal cell tumor. Epigenetics can also affect fetal development, birthweight, and insulin resistance and cardiovascular disease.\textsuperscript{96} Imprint abnormalities have been reported to be more common in children born by ART than in children born by natural conception.\textsuperscript{97,98} In ART pregnancy, it is clear that the neonatal birthweight increases after blastocyst transfer rather than cleavage embryo transfer, and after frozen-thawed embryo transfer compared with fresh embryo transfer.\textsuperscript{99,100} Imprinting occurs mainly at the stage of gametogenesis, fertilization, and early embryo development.\textsuperscript{95,101-107}
So, there are concerns that the effects of reproductive medicine on epigenetics such as ovarian stimulation, in vitro maturation, in vitro fertilization, culture conditions, and cryopreservation are affected. However, a pilot study has found that DNA methylation errors in imprinted genes in children born after ART have not been apparent, and infertility treatment does not cause imprint abnormalities, but patient background required infertility treatment is involved in epigenic changes. On the other hand, most ART-related mutations in pre- and postnatal methylation occur independently of embryo culture, and the epigenetic birth-related ART-related mutations in pre- and postnatal methylation occur in dependent of embryo culture, and the epigenetic birth-related changes associated with ART are largely resolved by adulthood. These suggest that epigenetics is involved with ART. Further research is needed to avoid the risk of epigenetic changes due to ART and to confirm that ART is not associated with child epigenetic changes.

7 | FOR MORE INFORMATION

There is a technique called preimplantation genetic testing (PGT) that has been made possible by the developments of reproductive technologies and genetic analysis. PGT is a method of genetically evaluating an embryo by performing an embryo biopsy prior to transfer to the uterus. There are three categories of preimplantation diagnosis: preimplantation genetic testing for monogenic / single gene defects (PGT-M), preimplantation genetic for diagnosing embryonic chromosomal structural abnormalities against the background of recurrent miscarriage of translocation carriers testing for structural rearrangement (PGT-SR), and preimplantation genetic testing for aneuploidy (PGT-A) for the purpose of embryo transfer without chromosomal abnormalities, especially chromosomal numerical abnormalities, with the aim of improving implantation rates and reducing miscarriage rates. Since indication and operation rules differ depending on the countries or regions, counseling for them varies depending on the rules in the countries or regions. The most important thing seems to be the provision of medical services without any disadvantage for clients who need medical technology. Counseling is required to accurately understand the information that most patients need.

8 | CONCLUSION

The genetic counseling is important for couples undergoing infertility treatment to understand the genetic background and unclear points of ART. It is important for the couples to know in advance the risk of birth defects and chromosomal abnormalities that are born with a certain probability, and it is also necessary for the medical staffs who provide reproductive techniques to understand that as well. The genetic counseling is often provided by genetic experts; however, reproductive staffs also require standard knowledge of genetics. Prior to ART, patients should be able to receive standard information about the genetics of ART equally and accurately.

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Conflict of interest: The authors declare no conflict of interest. Human/Animal rights: This article does not contain any studies with human and animal subjects performed by any of the authors.

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