In the past 20 years, a significant improvement has been shown in the treatment for infertility in both women and men through the development of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Only donated sperm could be previously used for treatment; now oocytes can also be donated. Furthermore, the combination of IVF and ICSI with advanced genetic methods has made preimplantation genetic diagnosis possible for many genetic conditions. These methods enable genetic testing of the early human embryo by using only a single cell, one blastomere biopsied from the embryo, as the sample from which the diagnosis of many chromosome rearrangements and other inherited diseases can be made. It has also been established that a considerable proportion of infertility is caused by genetic defects, which have several implications for infertility treatment. The purpose of this review is to give a concise introduction on how genetics is involved in assisted reproduction technology to specialists who may not be working in this particular field of gynecology, but who would need some knowledge of this for proper care of their patients.

Key words: genetics; ICSI; infertility; IVF; PGD

Submitted 11 June, 2004
Accepted 13 October, 2004

Introduction

The treatment for infertility, which is experienced by one in 10 couples (1,2), has greatly changed during the past two decades because of the development of in vitro fertilization (IVF) and more recently of intracytoplasmic sperm injection (ICSI). During the same period, methods to study the human genome have also advanced enabling the identification of a growing number of individual genes and thereby the molecular genetic etiology of many inherited diseases. In the past, the study of genetics in reproductive disorders was difficult, because these studies were based on familial occurrence of diseases. Yet, many reproductive diseases have a genetic background, and the number of those with a molecular genetic mechanism known at the DNA level is increasing. In a recent study, 24% of men with azoospermia or severe oligozoospermia have been shown to
carry a genetic abnormality (3). When treating these patients, the new assisted reproductive technology (ART) methods have potentially enabled the inheritance of infertility and certain other genetic conditions to the offspring. If, however, the genetic etiology is known before treatment, the risk for the offspring can be identified and prenatal or preimplantation genetic testing can be offered when appropriate (4).

The developments in ART and genetics have resulted in advanced knowledge of the genetic etiology in infertility. Moreover, genetic testing methods are increasingly exploited in ART and vice versa. A good example of this is preimplantation genetic diagnosis (PGD) in which IVF is used in order to avoid the recurrence of a specific genetic disease. But genetic testing, in the form of aneuploidy screening (AS), can also be used in order to improve the results of IVF. Clearly, the interface between genetics and reproductive medicine is rapidly growing. The aim of this article is to give a concise overview on how genetics is involved with ART particularly to those specialists, who do not need to address these issues in their daily work. We briefly discuss the genetic causes of infertility, how ART (in the form of gamete donation and PGD) is used in families with an inherited disease, and the consequences of ART treatments to the offspring.

Genetic causes of infertility

Chromosome aberrations

Sex chromosome aberrations are by far the best-known genetic causes of infertility in women and men. Hypergonadotropic primary amenorrhea is frequently caused by X chromosome aberrations, of which 45,X is the most common. However, mosaicism or structural abnormalities of the X chromosome are found in 50% of patients with Turner’s syndrome with often milder phenotypes with secondary amenorrhea or premature ovarian failure (5). Because chromosome studies are more frequently performed in patients with infertility, it is common to find sex chromosome abnormalities only in a small fraction (<10%) of studied cells. Very often, it is not possible to determine whether or not these findings are relevant to infertility or to its treatment.

Chromosome aberrations occur with a frequency of 1.9–12% in infertile men (6–9) and are most common in men with azoospermia or severe oligozoospermia (10–12). The most frequent chromosome aberrations associated with infertility in men are translocations and numerical sex chromosome aberrations, such as Klinefelter’s syndrome (47,XXY) (11).

In men with Klinefelter’s syndrome, donated sperm was previously used. More recently, testicular sperm extraction (TESE) with ICSI has enabled the use of the patient’s own sperm cells with subsequent pregnancies (13). In the future, the same may become feasible for the patients with Turner’s syndrome, because it has been shown that many young girls with Turner’s syndrome have ovarian follicles (14). If biopsied and frozen, these follicles could, perhaps, later be used in order to treat patients with their own sperm cells (15,16). Successful autotransplantation of cryopreserved human ovarian strips into the remaining ovarian tissue has already been performed in cancer patients (17,18). Scientific programs to study this treatment in Turner’s syndrome patients are presently under way. Using patients’ own sperm cells to treat patients with sex chromosome aberrations has also raised questions of an increased risk for the offspring. Presently, it seems that, although there may be a somewhat higher risk, further studies are needed in order to clarify this.

The most common recurrent chromosome translocation is the Robertsonian translocation between chromosomes 13 and 14 (Fig.1). It is also the translocation most frequently associated with infertility in men and disturbances of spermatogenesis, although it has not been unequivocally proved that it is the inherent cause of infertility in carrier men. In women, balanced chromosome translocations do not usually cause disturbances of ovarian function, unless X chromosome is involved, but infertility may be caused by recurrent spontaneous abortions because of unbalanced forms. Apart from possible infertility, the carriers of balanced translocations are healthy. For the offspring, there is, however, a varying risk of an unbalanced translocation with a severe phenotype, including congenital malformations and mental retardation. The risk of an unbalanced form in babies born to translocation carriers varies and is low for some translocations, for rob(13;14) approximately 1%, but up to 20% for some other Robertsonian translocations (19). In all cases, the identification of translocation carriers is important, because prenatal diagnosis or preimplantation genetic testing and often both are available. Additionally, recent studies on embryos from PGD cycles (20,21) and spermatozoa from translocation carriers (22) have shown a much higher frequency of aneuploidy than is known to occur in full-term pregnancies. Because many of these result in early miscarriage, translocations also affect the results of infertility treatment.
When parental karyotyping shows normal results, there may still be a slightly higher risk for chromosome rearrangements in children born after ART, particularly when ICSI is used. This is supported by the finding that some infertile men with a normal lymphocyte karyotype have a high frequency of chromosomally abnormal spermatocytes (23).

**Y chromosome microdeletions**

An obvious risk of ICSI treatment is the inheritance of male infertility. Large deletions (loss of genetic material) of the Y chromosome were first demonstrated in azoospermic and oligozoospermic men (24). Subsequently, it has been shown that small submicroscopic deletions in Y chromosome are found in 8.2% of infertile men (25). These are called microdeletions, because they are unidentifiable in normal karyotyping and have to be specially tested for (25). The microdeletions cause spermatogenetic failure because of the loss of spermatogenesis-controlling genes in the deleted regions. The frequency is highest in azoospermic or severely oligozoospermic men and very low in men with sperm counts of over $5 \times 10^6$/ml. The deletions usually arise *de novo* in the sperm and have not been inherited from a fertile father in naturally conceived pregnancies (26). However, once a deletion has occurred, it will be inherited by all male offspring.

The availability of ICSI for the treatment for male infertility has inevitably increased the risk of transmitting male infertility from father to son. Kent-First et al. (27) found that 9% of sons born after ICSI had Y chromosome microdeletions. In order to avoid the inheritance of a microdeletion, most couples prefer PGD, whereas some request treatment with donor sperm (28,29). In order to assess the fertility of children born from ICSI pregnancies, follow-up studies should be performed until adulthood.

**Single-gene disorders**

Presently, it seems that the most common conditions causing infertility in women, such as PCOS or endometriosis, are complex diseases with heterogeneous etiology (30,31). This means that several genes and environmental factors may play a role in the etiology and these factors may differ in various families and patients as well as populations. In familial clustering of PCOS, some inherited risk alleles have been identified, such as CYP11A (32–34). However, probably because of their complexity, major genes for these conditions have not yet been found.

In a small number of patients, infertility is caused by mutations in genes coding for hormones or hormone receptors, such as androgen receptor, LH and LH receptor, or follicle-stimulating hormone (FSH) and FSH receptor (35–37). Although patients with identified mutations have been described in all of these genes, they only explain but a small fraction of reproductive failure on the whole. However, mutations in some other known genes are more frequent in many populations and therefore the possibility of these mutations has to be considered in the present-day practice. These include mutations in the...
cystic fibrosis transmembrane conductance regulator (CFTR) gene in relation to male infertility and mutations in the \textit{FMR1} gene in relation to female infertility.

Cystic fibrosis (CF), one of the most common recessively inherited diseases in man, is caused by mutations in the \textit{CFTR} gene and normally presents with a severe phenotype with both lung and endocrine symptoms. Men with CF are infertile because of the failure of normal development of the vas deferens (38). Some \textit{CFTR} mutations are associated with a limited phenotype of congenital bilateral aplasia of the vas deferens (CBAVD) without other evident signs of CF (39,40). It has been estimated that most cases of CBAVD without other manifestations are related to \textit{CFTR} defects (41,42). Men with CBAVD are often compound heterozygotes who carry one of the common mutations in one allele of the \textit{CFTR} gene and a ‘milder’ mutation in the other. Infertility can be treated with aspirated sperm easily obtained by means of percutaneous epididymal sperm aspiration or TESE in local anesthesia. If the partner is a healthy carrier of a \textit{CFTR} mutation, there is a risk of both CF and CBAVD for the offspring. Approximately one in 22–28 persons in many Caucasian populations is CF carrier. Although more than 500 mutations have been found in the \textit{CFTR} gene, screening for the three most common mutations in the Scandinavian population will detect approximately 60–95% of CF carriers (43).

Fragile X syndrome is the most common disorder causing X-linked mental retardation. The syndrome is caused by a dynamic mutation, an expansion of a CGG trinucleotide repeat sequence (normally <60 repeats) in the \textit{FMR1} gene. When the expansion exceeds >200–230 repeats (full mutation), the gene is inactivated causing the syndrome. This expansion typically occurs when the mutation is inherited from a healthy mother, who is a carrier of a so-called pre-mutation (60–200 repeats), but not when the pre-mutation is inherited from a healthy father. Women who carry a pre-mutation are otherwise healthy, but approximately 10–15% of them develop premature ovarian failure (POF) (44,45). Therefore, women with POF of unknown origin should be informed of the possibility of having genetic testing for \textit{FMR1} mutations. Testing is particularly important, if a woman with POF intends to use donated oocytes from her sister who would also be at risk of being a carrier, if a pre-mutation is present in the family. PGD is also available for carrier women.

**ART in families with an inherited disease**

**Gamete donation**

A genetic disorder may cause a total deficiency of germ cells and infertility for the couples. In other families, carriers of a genetic abnormality are at the risk of transmitting an inherited disabling disease to the offspring. In both cases, donated gametes may be used in assisted reproduction in order to help the couples obtain a healthy child. Donor insemination has been performed for decades while the first successful treatment with donated oocytes was performed in 1984 in Australia (46).

If there is a total lack of functioning eggs or sperm, the only chance of conception is to use donated gametes. This is mostly the case in patients with Turner’s syndrome, Klinefelter’s syndrome or women with an \textit{FSH} receptor mutation. Women with Turner’s syndrome have as good a success rate in oocyte donation (OD) programs as other patients with ovarian failure (47–49). Excellent pregnancy results have also been shown in patients with an \textit{FSH} receptor mutation (50).

Prenatal testing and PGD are available for an increasing number of inherited diseases, but not for all. In those cases where prenatal testing is not available, ART with donated gametes is a good option for carriers of a genetic disorder in order to avoid transmission of a disease that might cause significant morbidity in the child. Many couples prefer donated gametes to their own in order to avoid termination of pregnancy, which they find unacceptable. OD is used, if the woman is a carrier of an autosomal dominant disease (e.g. tuberosis sclerosis) or an X-linked disease (e.g. X-chromosomal mental retardation of unknown genetic background). Donated oocytes are always needed in order to avoid mitochondrial diseases (e.g. Leigh disease or MELAS), because these disorders are always inherited from the mother and prenatal diagnosis for mitochondrial diseases is currently not possible. However, only 3% of all OD treatments are performed because of an increased risk of an inherited genetic disease (51).

When a man is a carrier of an autosomal dominant disease, donated sperm can be used. If both parents are carriers of an autosomal recessive disease (e.g. CF or recessive polycystic kidney disease), the risk of having an affected child is 25%. In these cases, it is possible to use donated oocytes or sperm or even donated embryos (52). Certainly, the development of PGD will reduce the need for gamete donation in these cases.
PGD involves performing genetic testing on an embryo obtained through IVF treatment. PGD was first introduced as a method for genetic testing of inherited diseases in 1989 and it is estimated that over 1000 healthy children have been born after PGD (53). Compared to conventional prenatal diagnosis, chorion villi sampling (CVS) and amniocentesis, PGD enables couples to avoid the termination of affected pregnancies, because only healthy embryos will be transferred. PGD may be used in order to study chromosome disorders and single-gene defects, when the mutation in the family is known, as well as for sexing in X-linked diseases (54). In order to perform PGD, one to two cells (blastomeres) are biopsied usually from a six- to eight-cell embryo 3 days after oocyte retrieval (Fig. 2). Alternatively, polar body biopsies may, sometimes, be removed and they may be tested. Fluorescence in situ hybridization (FISH) is used in order to study chromosomes (Fig. 1), whereas polymerase chain reaction (PCR)-based techniques are used for molecular genetic testing. In the last ESHRE report (55), a total of 2100 PGD cycles from 1561 couples have been reported in Europe. Excluding aneuploidy and social sexing screening, 1197 cycles of PGD resulted in 222 pregnancies (clinical pregnancy rate: 18.5% per oocyte collection). Recently, Verlinsky et al. reported the birth of 754 babies from PGD pregnancies in three participating centers in the US and Italy with a 25% overall pregnancy rate per embryo transfer (56). PGD has already been performed in many single-gene disorders, some of which have been listed in Table I. In trinucleotide repeat diseases, such as Fragile X syndrome, PGD is less complicated, because the mutation is always located in the same spot within the gene. For many other disorders, the analysis has to be designed for the specific mutation(s), which has been identified in the family. Although the diagnosis is based on a sample of one to two cells only, the overall rate of false diagnosis was 1.8% – 0.9 for FISH studies and 3.4% for molecular genetic testing (53). PGD babies were not found to have more neonatal problems or malformations than ICSI babies. Although the risk of false diagnosis seems low, confirming prenatal testing is still recommended in PGD pregnancies.

PGD is an option, if termination of a possible pregnancy is not acceptable for the couples. In these situations, the patient needs IVF treatment in order to perform PGD regardless of normal fertility. PGD is particularly suitable when a couple need IVF or ICSI treatment for infertility and there is a risk of genetic disease in the offspring, a situation that arises in chromosome translocations associated with male infertility. However, with FISH, only certain chromosomes can be studied at a time, whereas conventional karyotyping from CVS or amniocentesis gives more detailed information of the fetal karyotype.

**Table I. Examples of monogenic diseases for which preimplantation genetic diagnosis (PGD) has been performed**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis (CF)</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>β-thalassemia</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Tuberculous sclerosis</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>X-linked</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>X-linked</td>
</tr>
</tbody>
</table>

**Fig. 2.** A schematic presentation of preimplantation genetic diagnosis (PGD). After in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), embryo biopsy is performed on day 3 on six- to eight-cell embryos. One or two blastomeres are removed for genetic analysis with fluorescence in situ hybridization (FISH) for chromosome studies and for polymerase chain reaction (PCR)-based analysis for molecular genetic testing. Embryo transfer is performed on days 3–5.
The importance of age on ART results is well documented. Tan et al. (57) reported a cumulative live birth rate of 45% after five IVF treatment cycles among women aged 20–34, compared to that of 14.4% in patients aged >40. The suggested main reason for this change in fertility is a decline in oocyte quality, whereas uterine aging is thought to be of less importance. This conclusion is supported by the finding that older women failing to conceive with their own oocytes can be successfully treated by using oocytes donated by younger women (58,59). Furthermore, an increased rate of chromosome abnormalities has been reported in oocytes from older women (60,61). This seems to be because of abnormalities of the meiotic spindle occurring in 79% of oocytes from naturally cycling women older than 40 years, but only in 17% of oocytes from women under 25 years. Embryo morphology, developmental rates, and maternal age also seem to be correlated with chromosome abnormalities, indicating that the implantation failure in older women could be because of aneuploidy (62).

PGD can be used in order to enhance the IVF success in patients with advanced age by avoiding the transfer of chromosomally abnormal embryos. This is called AS. Individual embryos are biopsied and biopsy samples are examined for numerical chromosomal abnormalities by using 5–14 FISH probes. In several studies, Verlinsky et al. (63,64) found an increased chance of childbirth by using PGD–AS in patients of advanced maternal age. A study by Munne et al. (65) investigating the efficacy of PGD–AS in patients of >35 years showed a 2.5-fold decrease in spontaneous abortion rates, from 23% per patient in the control group to 9% in the PGD–AS group. This resulted in a significantly higher ongoing pregnancy rate in the PGD patients, compared to that in the controls.

In another study from Bologna, Italy (66), poor prognosis patients (maternal age: >36 years, failed IVF cycles, or maternal chromosomal abnormality) were allocated to two groups based on the patient's own decision to undergo PGD–AS. In total, 60% of the embryos showed chromosomal abnormalities. The pregnancy rate per started and transfer cycles was 29 and 37% in the PGD group, compared to 25 and 27% in the control group (without PGD but with assisted hatching). The implantation rate was significantly higher (24 versus 12%) in the PGD group, suggesting that there was an overall benefit to the poor prognosis patients, although this did not apply to those with earlier IVF failures. Similar results are seen in the ESHRE consortium data (55). These showed a 28% pregnancy rate both for maternal age of >35 years and for couples with recurrent miscarriages, but only a 7% pregnancy rate for couples with repeated IVF failures. These results indicate that among couples with recurrent IVF failures reasons other than chromosomally abnormal embryos are likely to cause the infertility problem.

Despite the fact that chromosome abnormalities cause embryo wastage and are reflected in decreased implantation and increased miscarriage rate, the studies thus far published on PGD–AS are somewhat disappointing. The possible reasons for this include a negative effect of the biopsy, the restricted number of analyzed chromosomes, and factors other than chromosomal that may influence the outcome in older women. Therefore, controlled studies by using strict randomization to clarify the possible benefit of PGD for chromosomal screening are urgently needed.

**Consequences for the offspring**

**Malformations**

The majority of early studies have been reassuringly negative, as far as congenital malformations in children born after conventional IVF are concerned (67–72) (Table I). However, comparison in the frequency of malformations has often been made with the general population, not with defined control groups. In the largest controlled study, comprising 9111 infants born after IVF (82%) and ICSI (18%) in Sweden, an excess of congenital malformations was found (5.6%, OR = 1.47, 95% CI = 1.34–1.61) (73). However, this excess disappeared when confounders, such as year of birth, maternal age, parity, length of infertility, and singleton/multiple birth, were considered. In the Swedish studies, a three-fold increase was found in the prevalence of some specific malformations, i.e. neural tube defects, gastrointestinal atresias, and omphalocele among IVF children and hypospadias among ICSI children, compared to that among spontaneously conceived controls (73–75). The increased number of hypospadias was observed only after ICSI for paternal subfertility.

The first 1987 children born as a result of ICSI have been meticulously studied and reported by the originators of ICSI in Brussels, Belgium. Their reported 2.3% rate of major malformations does not significantly differ from that of the general population in Belgium (76). However, in an Australian reanalysis of one of the early Belgian studies, a four-fold excess of major cardiovascular...
defects was found in ICSI children (77). In another Australian study, the malformation rate in IVF and ICSI pregnancies was similar (2.5%) (78).

An Australian study (79) compared the prevalence of major birth defects in children born after ICSI, conventional IVF and spontaneous conception. By the age of 1 year, 8.6% of ICSI children and 9% of IVF children had at least one major birth defect diagnosed, compared to 4.2% of children born after spontaneous conception. After adjustment for confounders, children conceived through ICSI and IVF were twice as likely to have a birth defect. An excess of malformations was also observed, when only singleton or term singleton births were considered. Although the rate of birth defects after ART in this study is alarmingly high, the study population was small and there were also some demographic differences, which could have influenced the results. A recent study from Belgium found comparable rates of major malformations in children born after ICSI (3.4%) and after IVF (3.5%) (80). Total rate of major malformations was 4.2% in ICSI and 4.6% in IVF, when stillborns and terminations were also included. Similar results were reported in a Norwegian study with a malformation rate of 5.42 and 5.14% in ICSI and IVF, respectively (81). Subsequently, two recent European studies have shown a small increase in the overall congenital malformation rate in children born after IVF and ICSI (82,83). The Dutch study showed a small increase in overall congenital malformation rate for children born after conventional IVF, compared to that for spontaneously conceived children (OR = 1.20, 95% CI = 1.01–1.43) (82). However, the result was not significant after the correction for differences in the study groups (OR = 1.03, 95% CI = 0.86–1.23). The prospective study from Germany reported an 8.6% rate of major malformations in the ICSI cohort and 6.9% in the spontaneous control group (OR = 1.25, 95% CI = 1.11–1.40) (83).

In conclusion, the results of controlled studies show a slight increase in congenital malformations after ART, some of which is probably related to parental characteristics and to the excess of preterm and multiple births. The risk caused by multiple births could be avoided by single embryo transfer, which has shown favorable pregnancy results (84). The absolute risk of serious congenital malformations in association with IVF/ICSI seems to be small. Results from studies of congenital malformations in IVF/ICSI children have been presented in Table II.

### Chromosome aberrations

In Danish and Swedish national cohort studies consisting of mainly children born after conventional IVF, no increase in chromosome aberrations was reported (72,73). Contrary to this, some early reports (85,86) showed alarmingly high frequencies of chromosome aberrations in small selected ICSI populations. The recently published data from the Belgian group showed that, among 1586 prenatal tests, 3.0% were abnormal (80). Of these, 1.4% were inherited chromosome aberrations from one of the parents. In a study from Egypt, abnormal karyotypes were found in 3.5% of 430 ICSI babies, compared to none in 430 babies conceived naturally (87). Based on these results, there seems to be a moderate excess of chromosome aberrations following ICSI, compared to approximately 1% described in neonatal populations (88,89). However, at least some of the excess of risk is associated with maternal age or male infertility rather than with the ICSI procedure itself. The results from chromosome studies in ICSI pregnancies and children have been presented in Table III.

### Epigenetic inheritance

Epigenetic inheritance refers to the phenomenon by which the function of genes is affected by mechanisms other than those affecting the DNA sequence itself. These involve mechanisms, such as DNA methylation and histone modification (90). These mechanisms control the expression of certain genes according to their origin in either the oocyte or the spermatozoa – that is, for normal development some genes need to be repressed when inherited from the mother and active when inherited from the father or vice versa. This form of epigenetic modification is called maternal or paternal imprinting according to the parental allele, which is silenced. Presently, it is estimated that there are some 50 human genes that undergo imprinting, typically involved in the control of growth.

Imprinting has to be reversible when genes are inherited through successive generations. This is accomplished first by erasing the epigenetic programming in germ cells when these enter the gonads (90) where after gamete specific imprinting occurs during sperm and oocyte development. Another phase of epigenetic modelling takes place in the early preimplantation embryo; however, this does not affect genes imprinted during gametogenesis. Because ART involves the handling of gametes and early embryos, a possibility of interfering with epigenetic programming has...
been raised (91–93). This is suggested by the finding that the large offspring syndrome in sheep seems to be because of imprinting defects and by the preliminary finding that two human malformation syndromes, Angelman’s syndrome (94,95) and Beckwith–Wiedemann syndrome (96–98), are suggested to be more prevalent in children born from ART pregnancies than in controls. In a proportion of patients, these two syndromes are caused by imprinting defects.

Because many imprinted genes are involved with the control of growth, they have also been suggested to have a role in tumor development. While some early reports based on small material showed an increased risk of congenital and embryonal tumors, subsequent controlled studies have not found an increase in childhood cancer in ART children, although this is, perhaps, controversial for retinoblastoma (74,99–101).

Although it is too early to conclude of the possible risk of imprinting disorders related to ART, it now seems low for a person. It is clear, however, that much more research is needed on this. Additionally, some of the effects may not be present but later in adult life, in which case it may take many years before reliable information can be obtained.

Conclusions
It is increasingly evident that the rapidly growing fields of reproductive medicine and molecular

---

Table II. Malformation rate in children born after in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI)

<table>
<thead>
<tr>
<th>Country</th>
<th>Children (number)</th>
<th>Malformation rate (%)</th>
<th>Control group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (64)</td>
<td>1581</td>
<td>2.2</td>
<td>–</td>
</tr>
<tr>
<td>Israel (66)</td>
<td>1419</td>
<td>2.2</td>
<td>–</td>
</tr>
<tr>
<td>France (65)</td>
<td>13 380</td>
<td>2.5</td>
<td>–</td>
</tr>
<tr>
<td>World Report (68)</td>
<td>19 869</td>
<td>2.1</td>
<td>–</td>
</tr>
<tr>
<td>Denmark (69)</td>
<td>2245†</td>
<td>4.8</td>
<td>4.6</td>
</tr>
<tr>
<td>USA (67)</td>
<td>25 059†</td>
<td>1.6</td>
<td>–</td>
</tr>
<tr>
<td>Sweden (70)</td>
<td>911†‡</td>
<td>5.6§</td>
<td>–</td>
</tr>
<tr>
<td>Belgium (98)</td>
<td>2 840 ICSI</td>
<td>3.4</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2 955 IVF</td>
<td>3.8</td>
<td>–</td>
</tr>
<tr>
<td>Australia (76)</td>
<td>301 ICSI†</td>
<td>8.6¶</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>837 IVF**</td>
<td>9.0</td>
<td>–</td>
</tr>
<tr>
<td>The Netherlands (79)</td>
<td>4224 IVF</td>
<td>††</td>
<td>–</td>
</tr>
<tr>
<td>Germany (80)</td>
<td>3372 ICSI</td>
<td>8.6‡‡</td>
<td>6.9</td>
</tr>
<tr>
<td>Finland (99)</td>
<td>304§§</td>
<td>6.6¶¶</td>
<td>4.4</td>
</tr>
<tr>
<td>Norway (78)</td>
<td>553 ICSI</td>
<td>–</td>
<td>5.42</td>
</tr>
<tr>
<td></td>
<td>1 731 IVF</td>
<td>–</td>
<td>5.14</td>
</tr>
</tbody>
</table>

*8% ICSI.
†32% ICSI.
‡18% ICSI.
§OR = 1.47 (95% CI = 1.34-1.61) versus control group.
¶OR = 2.0 (95% CI = 1.3-3.2) versus control group.
**OR = 2.0 (95% CI = 1.5-2.9) versus control group.
††OR = 1.2 (95% CI = 1.01-1.43) versus control group.
‡‡OR = 1.25 (95% CI = 1.11-1.40) versus control group.
§§Not significant for all malformations; heart anomalies: OR = 4.0 (95% CI = 1.4-11.7) versus population-based control group.
¶¶One child born after ICSI.

Table III. Chromosome aberrations among intracytoplasmic sperm injection (ICSI)-conceived fetuses/babies reported in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tests (n)</th>
<th>De novo percentage (n)</th>
<th>Inherited percentage (n)</th>
<th>Total percentage (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>15*</td>
<td>33.3 (5)</td>
<td>0 (0)</td>
<td>33.3 (5)</td>
</tr>
<tr>
<td>82</td>
<td>71*</td>
<td>12.7 (9)</td>
<td>0 (0)</td>
<td>12.7 (9)</td>
</tr>
<tr>
<td>100</td>
<td>206*</td>
<td>2.9 (6)</td>
<td>0.5 (1)</td>
<td>3.4 (7)</td>
</tr>
<tr>
<td>72</td>
<td>149*</td>
<td>1.3 (2)</td>
<td>1.3 (2)</td>
<td>2.6 (4)</td>
</tr>
<tr>
<td>83</td>
<td>430†</td>
<td>Not available</td>
<td>Not available</td>
<td>3.5 (15)</td>
</tr>
<tr>
<td>77</td>
<td>1586*</td>
<td>1.6 (25)</td>
<td>1.4 (22)</td>
<td>3.0 (47)</td>
</tr>
<tr>
<td>101</td>
<td>142*</td>
<td>4.2 (6)</td>
<td>0 (0)</td>
<td>4.2 (6)</td>
</tr>
<tr>
<td>All</td>
<td>2599</td>
<td>–</td>
<td>–</td>
<td>3.6 (93)</td>
</tr>
</tbody>
</table>

*Prenatal testing.
†Neonatal testing.
genetics are providing a common arena shared by gynecologists and medical geneticists. Both clinical genetics and genetic testing – molecular and cytogenetic – are becoming an integral part of ART. Likewise, the new methods of ART have, in some cases, revolutionized genetic diagnostics by enabling procedures, such as PGD. Previously, ART had been an area of expertise for specialists in reproductive gynecology. In the present situation, one may ask to which extent a reproductive team has included, or has access to, a clinical geneticist experienced in counseling couples for genetic risks and interpretation of the results of genetic testing.

While many types of genetic testing are available, it is important to observe that also when related to ART, the decision of genetic testing has to be made by the person who is going to be tested. Accordingly, providing or withholding treatment must not depend on the person’s choice of whether to be tested or not. Professionals bear a great responsibility because people can only make informed decisions on the information they have been given and understand.

**Acknowledgments**

We express our gratitude to Dr Nina Horelli-Kuitunen, Medix Laboratories, Finland, for providing us with material for Figs 1 and 2. In addition, we thank Organon Nordic for making the writing of this study possible.

**References**

26. Page DC, Silber S, Brown LG. Men with infertility caused by AZFc deletion can produce sons by intracytoplasmic sperm injection, but are likely to transmit the deletion and infertility. Hum Reprod 1999; 14: 1722–6.


Address for correspondence:
Kristiina Aittomäki
Department of Clinical Genetics
Helsinki University Central Hospital
PO Box 140
FI-00029 HUS
Helsinki
Finland
E-mail: kristiina.aittomaki@hus.fi