Preface

Although treatment is the major goal in the control of genetic disease, like in other fields of medicine, this is not yet a reality for most of inherited conditions. Even with a dramatic advancement in the field of gene therapy, there are still not, unfortunately, many successful stories, to allow predicting its sound impact in the near future. Therefore, in the absence of radical treatment, prevention of genetic disorders is still one of the available options for genetically disadvantaged people. Among the measures for prevention, the avoidance of the birth of an affected child in couples at genetic risk has become a quite acceptable option in many populations. This is based on a population screening and prenatal diagnosis, and has been quite successful, resulting in an almost eradication of new cases of some genetic diseases from several Mediterranean and some large Meddle Eastern populations. However, this has generated an increasing number of abortions following prenatal diagnosis, leading to a growing concern and negative reaction in society to the preventive genetics programs. For example, some ethnic groups cannot accept any control measures regarding congenital diseases, because of pregnancy termination not being allowed due to social or religion reasons. Even in those communities where abortion is allowed, some couples have to experience two or more terminations of pregnancies before they can have a normal child. No doubt these families might require an alternative option to achieve their desired family size without the need for termination of pregnancy.

The present book is devoted to a principally new approach in prevention of genetic disorders, which avoids the need for prenatal diagnosis and termination of pregnancy. Accordingly, a novel concept of pre-pregnancy diagnosis, which is called preimplantation genetic diagnosis (PGD), is introduced, which is based on the control of the processes of the oocyte maturation, fertilization, and implantation, so to select and transfer back to patients only normal embryos, and achieve an unaffected pregnancy resulting in the birth of a healthy child. In this way, the couples at high risk of having an offspring with genetic disease have an option to control the outcomes of their pregnancy from the onset. So the place of this approach in the context of other approaches for prevention of genetic disorders available is discussed, together with other primary preventive measures, which may allow presently avoiding up to a half of congenital malformations presented at birth (Chap. 1). Although the option of PGD involves an ovarian stimulation and in vitro fertilization (IVF), the description of the available experience demonstrates that this has appeared to be an acceptable procedure in many ethnic groups all over the world.

In fact, PGD is now entering its third decade as an established procedure for genetics and assisted reproduction practices, with exciting new developments that are changing the whole concept of prevention of congenital disorders, to allow the couples at risk to reproduce as normally as possible without much fear of having an affected offspring. The availability of the practical experience of tens of thousands of PGD cases makes it necessary to update the current information provided to medical profession and patients on its accuracy, reliability, and safety to ensure a wider clinical application, an improved access to PGD services of those at need who may benefit greatly from this technology. The dramatic developments in PGD technology are obvious from more than 250 different conditions for which PGD have been applied, with over 99.5% accuracy in the leading PGD centers. There is also not any restriction in provision of PGD, which may presently be performed for any genetic condition, even if no relevant haplotypes are available, such as in cases that the conditions were first identified in one of the parents or only in the affected child.

So the present edition of the book updates the progress in prevention of genetic disorders to demonstrate the important place of PGD in primary preventive measures and its increasing role in providing the whole range of reproduction options to couples at risk. Because of the above improvements of PGD methods, Chaps. 2 and 3 are considerably updated to provide the basis for improved accuracy to be achieved not only in leading PGD centers but also worldwide. This includes the methods for both direct and indirect testing for mutations, as a more universal approach for tracing their inheritance, with special emphasis on PGD for de novo mutations, which has previously presented a real challenge. As we have presently accumulated the world's largest experience in this area, we present PGD strategies for different genetic disorders, determined by de novo mutations of maternal or paternal origin, with dominant, recessive, and X-linked modes of inheritance (Chap. 3). Although the emphasis is mainly on the laboratory aspects, some of the ethical, social, and legal aspects will also be briefly explored (Chap. 8).

Indications for PGD were also expanded, with current wider application of PGD for diseases with genetic predisposition, such as different cancers and cardiovascular disorders. The number of requests for PGD of these common disorders is increasing gradually, with the progress of identification of the predisposing genes, with extremely high penetrance, such as in breast and colon cancer. So the description of our experience of a few hundreds of PGD cases for this group of conditions, which resulted in detection and transfer of embryos free of cancer predisposing genes in as high as 80% of cases, with one-third of them yielding the unaffected pregnancies and birth of healthy children, will help initiating similar services in other centers, facing the forthcoming increase of requests from this highly sensitive group of at-risk couples (Chap. 3). This section also includes the first cumulative experience of PGD for inherited cardiac disorders, allowing couples carrying cardiac disease predisposing genes to reproduce without much fear of having offspring with these genes at risk for premature or sudden death.

Because of tremendous progress in PGD for stem cell transplantation treatment of genetic and acquired disorders, the special section devoted to

preimplantation nongenetic testing involving HLA typing is substantially updated based on our pioneering experience still representing one of the largest in the world (Chap. 4). Since our first description of such a possibility more than 10 years ago, PGD for HLA matching has been performed in a few thousands of cases, resulting in a successful HLA-compatible stem cell transplantation in close to 100 siblings, with almost 100% success rate. The list of conditions for which this approach was applied is being gradually extended, so the description of this experience will help to avoid the potential problems of the observed recombination in the HLA gene cluster, affecting the selection of HLA matched embryos, and the clinical outcome of stem cell transplantation. This will promote a wider application of the stem cell therapy, which will be reality for increasing number genetic and acquired conditions, for which there is still no available treatment.

Despite recent controversy in PGD for chromosomal disorders, the present progress in improving the accuracy of the procedure through the adequate choice of biopsy material and microarray analysis for 24 chromosomes has demonstrated the clinical impact of avoiding aneuploid embryos from transfer. A highly improved detection of chromosomally abnormal oocytes and embryos by microarray technology is currently being validated for practical application due to the obvious need for detecting and avoiding the chromosomally abnormal embryos from transfer as a standard practice, so this is described in detail in a special section, with detailed discussion of the present controversy on PGD impact on pregnancy outcome (Chap. 6). The presented preliminary data on 24 chromosome testing confirm our extensive original experience of FISH analysis of over 20,000 oocytes and embryos, which is presented with special emphasis on chromosome-specific prevalence in relation to maternal age, their meiotic origin, and its possible impact on embryo viability. Because 96% of aneuploidies originate from female meiosis, the primary emphasis is still on testing for 24 chromosomes in the first and second polar body by array-CGH. On the other hand, to detect mitotic errors and paternally derived aneuploidies, the technique is being validated also for blastocyst biopsy, evidencing the accuracy for detecting post-zygotic errors, including mosaicism, which is still the major challenge of PGD for chromosomal disorders by embryo biopsy (Chap. 5).

It is further confirmed that PGD is the only hope for couples carrying balanced translocations (Chap. 5). In the light of these data, a pioneering work on different conversion methods to turn interphase nuclei of single biopsied blastomeres into metaphase chromosomes is described with presentation of the original experience of the application of these methods for PGD of translocations. On the other hand, further improvement in PGD for translocations is being achieved by application of microarray technology, although its utility is limited to the cost.

In Chap. 7, the original experience on the applications of PGD to the embryonic stem cells is described, providing the possibility of obtaining preimplantation embryos with known genotypes as a source for the establishment of custom-made embryonic stem cells. This section provides the data on the establishment of the world's largest collection of the genetic disease-specific embryonic stem cell lines, containing 87 lines with genetic and

chromosomal disorders and 12 lines with the allele conferring resistance to HIV. This is the unlimited source and unique in vitro model for analysing the primary mechanisms of congenital disorders, and development of the methods for cellular therapy.

So the second edition provides extensive review of the most recent developments of PGD, which includes PGD for expanding indications, such as de novo mutations, cancers, inherited cardiac diseases and combined PGD for single gene disorders, HLA typing and 24 chromosome testing in patients of advance reproductive age, in the light of the further prospects of the application of PGD to medical practice. This may be useful not only in planning and organization of such services but will also provide a working manual for the establishment and performance of PGD in the framework of IVF and genetic practices.