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Preimplantation Genetic Diagnosis for Cancer

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Abstract

Preimplantation genetic diagnosis (PGD) is now an established approach for preventing genetic disorders, utilized for over 500 different genetic conditions and thousands of their causing mutations. If done according to the available guidelines, PGD for monogenic disorders is highly accurate and reliable, with close to 99% accuracy rate. A current wider application of PGD is due to its expanding use for common diseases, including inherited predisposition to cancer, the indication that has never been applied in prenatal diagnosis. The present paper describes our PGD experience for cancer, which is the world's largest series, including 452 clinical cycles that resulted in birth of 171 healthy children, without predisposing genes for cancer. This may demonstrate the practical value of PGD for primary prevention of inherited predisposition to cancer.

Introduction

Preimplantation genetic diagnosis (PGD) is presently incorporated into clinical practices as a powerful tool in preventing inherited disorders, which are still not responding to any available treatment [1-4]. Increasing number of PGD procedures is now being performed, allowing at risk couples to avoid the birth of children with genetic disorders, with the principle objective of achieving the birth of an unaffected babies, obviating a potential risk of pregnancy termination following prenatal diagnosis.

In contrast to prenatal diagnosis, PGD is also applied to the late-onset diseases with genetic predisposition. It is known that some patients with inherited pathological predisposition may even remain childless to avoid the risk of pregnancy termination after prenatal diagnosis. So PGD provides for them a realistic option for undertaking pregnancy, with a realistic chance of having healthy offspring with no risk to develop common disorders determined by the mutations which could have been inherited from parents [5]. The most frequent indication for PGD of diseases with genetic predisposition is cancer, which was first performed for Li-Fraumeni syndrome (LFS) and then applied for a variety of other cancers [6-14].

The present paper describes our experience of PGD for cancers, which is the world's largest series of 452 clinical cycles, demonstrating the utility of the approach as a preventive measure for inherited cancers.

Material and Methods

A total of 452 PGD cycles for 236 couples at risk for producing an affected progeny with inherited cancer were performed, which includes 20 cycles for 10 couples reported earlier [4,7] (Table 1).

As shown in Table 1, 18 different cancers were indications for PGD, the most frequent being breast cancer, BRCA 1&2 (124 cycles for 64 couples), neurofibromatosis, NF1 &2 (82 cycles for 47 couples), Fanconi anaemia, FA (70 cycles for 23 couples) and colon cancer, FAP (32 cycles for 17 couples), Retinoblastoma, RB1 (27 cycles for 14 couples), and tuberous sclerosis, TSC type 1 and type 2 (34 cycles for 24 couples). PGD for other 12 cancer conditions were performed in less than two dozens of cycles (see Table 1).

All PGD cycles were performed using a standard IVF protocol coupled with micromanipulation procedures for sequential first and second polar body (PB) (PB1 and PB2) sampling, and/or embryo biopsy, described elsewhere [14]. The biopsied PBs, blastomeres or blastocyst samples were tested by the multiplex nested PCR analysis, involving the above mu-

tations and linked marker analysis in a multiplex heminested system [15,16]. The majority of cases were performed by embryo biopsy, which is presently done predominantly by blastocyst biopsy [15].

In cases of advanced reproductive age, 24-chromosome aneuploidy testing was performed, using next generation technologies (Illumina Inc), with a few described earlier done by FISH analysis (15). Pregnancy outcome was defined as the presence of a gestational sac with fetal cardiac activity.

As per the informed consent approved by IRB, the embryos derived from the embryos free of genetic predisposition to cancer, based on the mutation and polymorphic marker information, were pre-selected for transfer back to patients, while those with predisposing mutant genes were considered affected , and tested to confirm the diagnosis.

transfer) and birth of 171 cancer predisposition free children. Healthy children free from cancer predisposing genes were born following PGD for all but one condition (a single cycle for a couple with brain tumour). It is of note that the results of PGD were highly accurate with no misdiagnosis observed in testing of over two thousands embryos that may be recommended for a wider clinical application.

Presented data are currently the world's largest PGD series for cancers, involving couples at risk for producing BRCA 1 and 2, Li-Fraumeni syndrome (LFS), familial adenomatosis polyposis (FAP), familial colorectal cancer, hereditary nonpolyposis coli (HNPCC) (type 1 and 2), Von Hippel-Lindau syndrome (VHL), familial posterior fossa brain tumor (hSNF5), retinoblastoma (RB), neurofibromatosis 1 and 2 (NF1 and NF2), nevoid basal cell carcinoma (BCNS) or Gorlin syndrome, tuberous sclerosis (TSC type 1 and type 2), ataxia teleangiectasia (AT), multiple endocrine neoplasia type 1and type2 (MEN1 and MEN2), and Fanconi anemia (FANC) (Table 1).

Table 1. Preimplantation Genetic Diagnosis for Cancer

Disease	# Patient	# Cycle	# Transfers	# Embryo transferred	Pregnancy	Birth
AT*	2	4	3	4	2	1
BCNS(GORLIN)	5	6	5	9	3	3
BRAIN TUMOR	1	1	1	1	0	0
BRCA 1	42	69	40	68	26	32
BRCA 2	22	55	27	45	12	15
FANC	23	70	44	64	18	18
FAP	17	32	27	47	10	9
HNPCC 1	6	14	4	6	5	3
HNPCC 2	5	12	10	19	5	6
LFS	8	10	6	10	3	3
MEN1	5	17	12	19	5	5
MEN2	2	3	3	5	2	3
NF1	42	74	59	96	26	27
NF2	5	8	8	16	6	8
RB1	14	27	21	35	10	10
TSC1	20	27	21	41	14	18
TSC2	4	7	6	10	2	2
VHL	13	16	9	17	7	8
TOTAL	236	452	306 (68%)	512 (1.67)	156 (50.9%)	171

Results and Discussion

As seen from Table 1, of 452 PGD cycles performed for 236 at risk couples 306 resulted in transfer of 512 cancer predisposition free embryos (1.67 embryos per transfer, on the average), yielding 156 clinical pregnancies (50.9% pregnancy rate per

Although the majority of these disorders are relatively rare autosomal-dominant conditions, with prevalence of 1 in 5,000 or less, their cumulative prevalence is significant, representing a growing indication for PGD, representing in our experience, the largest group of conditions with genetic predisposition for which PGD was performed.

So the results show that PGD may be offered as a realistic option for couples at high risk for producing offspring with cancer, to avoid inheritance of the predisposing genes from parents. Clearly, the couples at risk will benefit from the information about such option, as if inheritance of these genes is not avoided, their offspring will be susceptible to cancer, that may manifest at either at the early childhood, or later in adult life.

This makes it important to incorporate the family history into the clinical settings to identify any information about family members with cancer that may indicate to a possible candidates requiring PGD. Of course, the chances of their offspring to develop the disease will differ depending on the mode of inheritance and other risk factors, but the risk that this will lead to cancer cannot be excluded, justifying parents' requests for PGD. In addition, the personal experience of the couple is of particular importance, altering the family's perception of severity of the problem as the basis for their decision to undertake PGD. It may be recommended that one of the potential at risk groups to benefit from such information may be the couples undergoing IVF for fertility treatment, as PGD could be provided within the framework of IVF to avoid the inheritance of genetic susceptibility factors.

It should be mentioned, that the information about cancer in the extended family tree may not always be available, so the future implementation of preconception screening programs for identification of carries of genes predisposing to cancer might be of great utility for applying PGD as a useful tool for avoiding the risk for producing offspring with inherited cancer at their lifespan.

As in other common disorders with genetic predisposition, PGD for cancer has also important ethical implications, as most of these conditions are not present at birth, and may not be realized even during the lifetime. So the couples at risk could be reluctant to use prenatal diagnosis for cancer, as pregnancy termination cannot be justified for this purpose. On the other hand, PGD seems to be ethically more acceptable, allowing couples to reproduce, establishing only pregnancy free from predisposing genes. This makes it important to provide genetic counselling services to inform patients at risk of having children with a strong genetic predisposition to cancer about the availability of PGD. Without such information these couples may remain childless because of their fear to opt prenatal diagnosis and possible pregnancy termination.

As can be seen from Table 1, PGD is being performed for increasing number of cancers, the majority of cycles resulting in birth of children free of predisposing genes. With current progress in understanding of the molecular basis of cancers, and sequencing of the genes involved in malignancy, the inherited cancer predisposition will soon become one of the emerging PGD indications, presently representing over 10% of our PGD experience for Mendelian disorders. As mentioned, despite extensive discussions of the ethical and legal issues involved in PGD for late onset disorders with genetic predisposition, an increasing number of patients regard the procedure not only as their favourable option but also the only possible reason for forgoing the pregnancy free of mutation from the onset. However, in cases when the female partner is a carrier of the genes predisposing to cancer, PGD with ART may increase their risk for developing cancer themselves, so they should be properly cancelled to have an option to opt against PGD or consider a surrogate mother.

Because such diseases present beyond early childhood and even later may not be expressed in 100% of the cases, the application of PGD for this group of disorders is still highly controversial. However, initial experience in offering PGD for this indication shows that the availability of PGD allows couples forgoing pregnancy, which otherwise would never be attempted.

In conclusion, we presented the world's largest PGD experience for cancer which shows that it is highly accurate, reliable and safe. The data suggest that PGD for cancer is of practical value, and may be recommended for wider application for primary prevention of inherited predisposition to cancer.

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