Hum. Reprod. (2012) 27 (suppl 2): ii74-ii76. This article appears in: Abstract book of the 28th ESHIRE Annual Meeting, Turkey 1 July – 4 July 2012
doi: 10.1093/humrep/27.s2.50

SESSION 51: PGD/PGS: LOOK TO THE PAST, PREPARE THE FUTURE

O-191 Feasibility of preimplantation genetic diagnosis for hereditary breast and ovarian cancer: report on a large cohort study

I.A.P. Derks-Smeets[1], W. Verpoest[2,] S. Mackens[2], P. Verdyck[3], G. Verheyen[2], A. Paulussen[1], J. Dreesen[1], R. Van Golde[4], V.C.G. Tjan-Heijnen[5], M. Meijer-Hoogeveen[6], E.B. Gómez García[1], J. De Greve[7], M. Bonduelle[3], C.E.M. De Die-Smulders[1] and M. De Rycke[3]

Author Affiliations

[1]*Maastricht University Medical Centre, Department of Clinical Genetics, Maastricht, The Netherlands*
[2]*Universitair Ziekenhuis Brussel, Centre for Reproductive Medicine, Brussels, Belgium*
[3]*Universitair Ziekenhuis Brussel, Centre for Medical Genetics, Brussels, Belgium*
[4]*Maastricht University Medical Centre, Department of Obstetrics and Gynecology, Maastricht, The Netherlands*
[5]*Maastricht University Medical Centre, Department of Internal Medicine, Division of Medical Oncology*
[6]*University Medical Centre Utrecht, Department of Reproductive Medicine and Gynecology, Utrecht, The Netherlands*
[7]*Universitair Ziekenhuis Brussel, Department of Medical Oncology, Brussels, Belgium*

Abstract

Introduction: Female carriers of a mutation in the *BRCA1* or *BRCA2* genes (*BRCA1/2*) have a lifetime risk of 60-80% to develop breast cancer and a risk of 30-60% (*BRCA1*) or 5-20% (*BRCA2*) for ovarian cancer. The late onset, reduced penetrance and availability of preventive and therapeutic options of this autosomal dominant disorder make prenatal diagnosis (PND) for *BRCA1/2* controversial. Preimplantation genetic diagnosis (PGD) offers a reproductive alternative. Up to now only three reports have described a total of five pregnancies after PGD for *BRCA1/2*. The safety of hormonal stimulation needed for IVF/PGD treatment in female *BRCA1/2* carriers has not been systematically studied so far.

Material and Methods: Asymptomatic female carriers were screened for occult malignancies of the breasts and ovaries before PGD treatment. Patients with a history of breast cancer were eligible for PGD if they were free of disease for at least two years after oncologic treatment. Embryos were derived from IVF using different protocols (i.e. GnRH

agonist or antagonist). ICSI was used to avoid contamination in the PCR analyses. Generic PGD-PCR tests were developed based on haplotyping of at least two flanking microsatellite markers on either side of the *BRCA1/2* loci. All markers were amplified on single blastomeres in a multiplex PCR run. Only in a minority of cases (< 10%) these generic tests were not applicable and a mutation specific protocol, including the private mutation and at least one informative marker, was set-up.

Results: 145 PGD cycles for *BRCA1/2* mutations were performed in 70 couples (mean 2.1 cycles per woman, SD 1.3): 59.2% represented female carriers of whom 66.7% had a *BRCA1* mutation. Mean female age was 29.6 years (range 22-40, SD 3.7). 26.2% of female carriers had undergone a prophylactic bilateral mastectomy. Of all fresh PGD cycles, 85.9% led to ovum pick-up (OPU). 717 embryos were eligible for genetic analysis (mean 5.78 per OPU). Of these, 43.1% were affected, 40.7% were unaffected and transferable, 9.9% had an abnormal genotype and in 6.3% the analysis was inconclusive. 62.1% of the PGD cycles led to primary embryo transfer (ET) and 3.6% to frozen ET of one or two unaffected embryos, resulting in 42 pregnancies in 40 women. Pregnancy rates were 41.4% per primary ET and 23.1% per frozen ET.

Six women had a history of breast cancer. Three of them underwent PGD on embryos cryopreserved before chemotherapy, resulting in two ongoing pregnancies.

Two *BRCA1* carriers were diagnosed with early stage triple negative breast cancer (T1N0 and T1N1), two and three months after PGD treatment respectively. One of them had a history of cancer in her contralateral breast. Another woman, a *BRCA1* carrier who underwent PGD for another indication, was diagnosed with breast cancer (T1N0) two months after PGD. None of these patients became pregnant after IVF/PGD treatment.

Conclusions: This cohort represents the largest number of PGD treatments for *BRCA1/2* mutations in Europe. PGD for *BRCA1/2* is feasible with relatively high pregnancy rates (29.0% per cycle started). Two female *BRCA1* carriers were diagnosed with breast cancer within three months after PGD treatment, despite breast screening shortly before. Larger observational studies are needed in order to elucidate whether this is a coincidental finding or a causal relationship can be found.

Full text:
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