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ABSTRACT

Introduction: Data on preimplantation genetic testing (PGT-M) in patients with genetic susceptibility to cancer are scarce in the literature, while there is, in our experience, a growing familiarity with assisted reproduction techniques (ART) among pathogenic variant heterozygotes. We performed a retrospective multicenter study of PGT-M outcomes among French patients with genetic susceptibility to cancer. Our objectives were to collect data on this complex issue, and to help cancer geneticists counsel their patients of reproductive age. We also wanted to increase awareness regarding PGT-M among cancer genetics professionals.

Material and methods: Patients from three university hospital cancer genetics clinics who had requested PGT-M between 2000 and 2019 were included retrospectively. Data were extracted from medical records. Patients were then contacted directly to collect missing and up-to-date information.

Results: Out of 41 eligible patients, 28 agreed explicitly to participate when contacted and were therefore included. They carried PV in *VHL* (n = 9), *APC* (n = 8), *CDH1* (n = 5), *STK11* (n = 2), *AXIN2*, *BRCA1*, *MEN1*, and *FH* (n = 1). Seven patients were denied PGT-M based on multidisciplinary team meetings or subsequently by the ART hospital teams, two changed their minds, and two were yet to start the process. PGT-M was successful in seven patients (25%), with a mean age at PGT-M request of 27. Most had von Hippel-Lindau. PGT-M failed in the remaining 10, with a mean age at PGT-M request of 32. The main reason for failure was non-implantation of the embryo. Of these, four patients were pursuing PGT-M at the time of last contact.

Conclusion: PGT-M outcomes in patients with cancer susceptibility syndromes were satisfactory. These patients should be informed about PGT-M more systematically, which would imply greater awareness among cancer genetics professionals regarding ART. Our series was not representative of cancer susceptibility syndromes in general; the predominance of cases with syndromes characterized by early-onset, highly penetrant disease is explained by the restrictive French guidelines.

Keywords: assisted reproduction techniques, familial adenomatous polyposis, genetic susceptibility to cancer, hereditary cancer, preimplantation genetic diagnosis, von Hippel-Lindau.

DECLARATIONS

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MAIN TEXT

Introduction

Data regarding preimplantation genetic testing (PGT-M) in patients with genetic susceptibility to cancer are scarce in the literature. Series were either published a long time ago, or are limited to a specific syndrome. Rechitsky *et al.* reported in 2002 a series of 20 PGT cycles in 10 patients, mainly with Li-Fraumeni and von Hippel-Lindau (VHL) syndromes, resulting in the birth of four unaffected babies [1]. In an Israeli study, Mor *et al.* observed a 26% uptake rate among heterozygotes for *BRCA1/BRCA2* pathogenic variant (PV) who were offered PGT-M [2]. Dutch geneticists reported the birth of 38 babies among 70 couples following PGT-M for a *BRCA1/BRCA2* PV [3]. Finally, hereditary breast and ovarian cancer (HBOC) was one of the top PGT-M indications in the last European consortium publication [4].

In our experience, there is a growing familiarity among PV heterozygotes with assisted reproduction techniques (ART) through social networks and the internet. It is legitimate to discuss PGT-M considering the morbidity and mortality associated with cancer susceptibility syndromes, and the potential risks in the offspring. Studies are therefore needed to assess access to PGT-M and outcomes among individuals at increased risk of cancer.

French national guidelines state that PGT-M can be considered when there is a very high risk of early-onset cancer (child, adolescent, young adult) with limited screening or risk-reduction possibilities, or when risk-reducing surgery has severe consequences [5]. However, these guidelines are non-binding, and do envisage PGT-M on a case-by-case basis in other, "less severe" syndromes, for example hereditary breast and ovarian cancer, if there is a particularly strong cancer family history. In practice, decisions are made locally during multidisciplinary team meetings involving a biologist or laboratory geneticist with expertise in PGT-M, a medical geneticist, a cancer geneticist, a gynecologist, and a genetic counselor.

We performed a retrospective multicenter study of PGT-M outcomes among French patients with genetic susceptibility to cancer. Our objectives were to collect data on this complex issue, and to help

cancer geneticists counsel their patients of reproductive age. We also wanted to increase awareness regarding PGT-M among cancer genetics professionals.

Materials and methods

Patients from three university hospital cancer genetics clinics were included: Hôpital Pitié-Salpêtrière and Hôpital Saint-Antoine (both with general cancer genetics activity and part of the Assistance Publique – Hôpitaux de Paris, Sorbonne Université network), as well as the PREDIR national reference center for patients with susceptibility to renal cell carcinoma (RCC) at Hôpital Bicêtre near Paris. Patients with a cancer susceptibility syndrome who requested PGT-M between 2000 and 2019 were included. According to French laws applicable to retrospective studies, they were informed in writing of the ongoing work, given the possibility to opt out, and told that they would soon be contacted. Ethics committee approval was not required given the nature of the study. Data were first extracted from medical records. Patients were then contacted directly by phone in October 2019 and again in October 2020 to collect missing and up-to-date information. We focused on the following points: molecular diagnosis, personal history of cancer, personal history of prenatal diagnosis (PND) and pregnancy termination, number of children, socio-professional category, how they first heard about PGT-M, first PGT-M request, PGT-M/PND multidisciplinary team decision, PGT-M feasibility, number of cycles and outcomes, and reasons for failure. Seven patients from the PREDIR network were previously included in a large paper on PGT-M but with a very technical focus, and no details or discussion regarding the clinical aspects or the specificities of cancer susceptibility syndromes [6]. Of note, no patient underwent PGT-A in association with PGT-M, as PGT-A is prohibited by French law.

Results

Forty-one patients were eligible. Twenty-eight agreed explicitly to participate when contacted and were therefore included. One patient refused to take part and 12 did not respond to our requests.

Of the 28 participating patients, nine were men and 19 were women. Nine carried a PV in *VHL* (32.1%), eight in *APC* (28.5%), 5 in *CDH1* (17.9%), two in *STK11* (7.1%), and one in each of the following genes: *AXIN2*, *BRCA1*, *MEN1*, and *FH* (3.6%). Nine had a personal history of invasive

cancer associated with their genetic syndrome (e.g. breast, colorectal, renal cell carcinoma, medulloblastoma), while all VHL patients had at least a history of hemangioblastoma or pheochromocytoma. They had mainly been treated with surgery, although one, an *APC* PV heterozygote, had received chemotherapy before PGT-M (see below). The MEN1 case had a history of parathyroid and pituitary adenoma, and of non-secreting neuroendocrine pancreatic tumor.

One patient was denied the procedure by the multidisciplinary team meeting because of her age (43 years old), and six were rejected at the following stage by the PGT hospital team. Of these six, four were rejected because of ovarian insufficiency. Insufficiency was actually diagnosed in partners of PV heterozygotes in three cases (ages 29, 32, and 39). The female patient with ovarian insufficiency was only 29 years old and had no history of cancer systemic treatment. Technical impossibility to perform PGT-M precluded the procedure in the other two. In addition, two patients changed their minds and did not proceed with PGT-M. One of them cited personal reasons. The other became pregnant spontaneously. She subsequently went ahead with prenatal diagnosis (PND); the fetus did not carry the PV. Finally, two patients were yet to start ovarian stimulation. That left us with 17 patients (Figure 1).

PGT was successful in seven (25%) of all patients, leading to the birth of 11 babies after a total of 16 cycles (Table 1). Mean age at PGT-M request in this group was 27 (age 23–31). Five patients had VHL, one familial adenomatous polyposis (FAP) with a history of risk-reducing total colectomy, and one multiple endocrine neoplasia type 1 (MEN1). None had received chemotherapy in the past.

PGT failed in the remaining 10 patients after a total of 16 cycles. Mean age at PGT-M request in this group was 32 overall (range 24–38). The main reason for failure was non-implantation of the embryo (number of cycles = 7). Other causes were the absence of embryos not carrying the PV (n = 3), embryo biopsy failure (n = 2), ovarian stimulation failure (n = 1), non-development of the embryo (n = 1), and chromosomal anomalies in the region of interest (n = 1). Details are given in Table 2. Of these, four patients were pursuing PGT-M at the time of last contact. The other six had abandoned the procedure for the following reasons: invasiveness and complexity of the process (n = 2), incident cancer (n = 2), ovarian insufficiency after the first cycle (n = 1), and separation (n = 1). Incident

cancers were a gastric adenocarcinoma in an *APC* PV heterozygote, and a non-epithelial gynecological cancer in a *STK11* PV heterozygote. Only one patient in this group had received chemotherapy prior to PGT-M, a female *APC* PV heterozygote with a history of total colectomy and synchronous colorectal cancers.

We asked the participants how they first heard about the possibility of undergoing PGT-M. The information had been provided by the geneticist in 15 patients (53.6%), another physician in six (21.4%), and through non-medical sources in five (17.9%). Two patients did not remember. We also documented the participants' socio-professional category, the most represented being "higher managerial, administrative and professional occupations" (n = 9, 32.1%).

Table 1: Patients in whom PGT-M was successful

Sex	Gene	Personal history of tumors associated with the genetic syndrome (age)	Age at PGT-M request	Number of cycles	Number of children born after PGT-M
M	*APC*	Multiple adenomatous colon polyps (risk-reducing total colectomy at 27)	29	1	1
M	*MEN1*	Parathyroid and pituitary adenomas (13), non-secreting neuroendocrine pancreatic tumor (28)	26	5	1
F	*VHL*	Multiple CNS hemangioblastomas (28) and retinal hemangioblastomas (10), bilateral renal cysts (19), multiple pancreatic cysts (14), paraganglioma (25)	26	2	1
M	*VHL*	Multiple CNS hemangioblastomas (19) and retinal hemangioblastomas (14)	30	3	3
F	*VHL*	Multiple CNS hemangioblastomas (13) and retinal hemangioblastomas (14), renal cysts (32), bilateral pheochromocytoma (15, 25), one pancreatic cyst (26), neuroendocrine pancreatic tumor (26)	24	3	2
F	*VHL*	Multiple CNS hemangioblastomas (20) and retinal hemangioblastomas (17), multiple clear cell RCC (20), multiple pancreatic cysts (26)	23	1	2
M	*VHL*	Multiple CNS hemangioblastomas (26) and retinal hemangioblastomas (32), bilateral renal cysts (26), pancreatic cysts (31), bilateral epididymal cysts	31	1	1

CNS = central nervous system, RCC = renal cell carcinoma

Table 2: Patients in whom PGT-M failed, with no completed pregnancy after at least one cycle

Sex	Gene	Personal history of tumors associated with the genetic syndrome (age)	Age at PGT-M request	Number of cycles	Cause of failure for each cycle	Current status
F	*APC*	Multiple adenomatous colon polyps (risk-reducing total colectomy at 31), 2 desmoid tumors (34)	34	1	- Non-development of the implanted embryo	Discontinuation: incident gastric cancer
F	*APC*	Multiple adenomatous colon polyps (total colectomy at 32), 2 colorectal cancers (32) treated with chemotherapy	32	2	- All embryos carried the PV - Failure of embryo biopsy	Further attempts planned
F	*CDH1*	Prophylactic gastrectomy (38), breast lobular carcinoma in situ (39)	38	1	- All embryos carried the PV	Discontinuation: invasiveness and complexity of the process
M	*CDH1*	Prophylactic gastrectomy (22)	31	2	- Implantation failure - All embryos carried the PV	Further attempts planned
F	*CDH1*	Prophylactic gastrectomy (33)	33	3	- Failure of embryo	Discontinuation:

					biopsy - Implantation failure - Unknown	invasiveness and complexity of the process
F	*STK11*	Multiple gastrointestinal polyps, breast ductal carcinoma in situ (32)	35	1	- Implantation failure	Further attempts planned
F	*STK11*	Multiple gastrointestinal polyps	24	1	- Implantation failure	Discontinuation: incident non-epithelial gynecological cancer
F	*VHL*	Multiple CNS hemangioblastomas (36) and retinal hemangioblastomas (39), bilateral clear cell RCC (36), multiple pancreatic cysts (36)	36	1	- Stimulation failure	Discontinuation: ovarian failure
M	*VHL*	Multiple CNS hemangioblastomas (32) and retinal hemangioblastomas (22), multiple clear cell RCC (22), bilateral pheochromocytoma (22), neuroendocrine pancreatic tumors (25), epididymal cystadenomas (22)	26	3	- Implantation failure - Implantation failure - Chromosomal anomalies warranting termination	Further attempts planned
F	*VHL*	Multiple CNS hemangioblastomas (34) and retinal hemangioblastomas (23), bilateral clear cell RCC (40), pheochromocytoma (40), multiple neuroendocrine pancreatic tumors (24)	34	1	- Implantation failure	Discontinuation: couple separation

Discussion

In this retrospective series focusing on outcomes of PGT-M in patients with genetic susceptibility to cancer, 25% gave birth to at least one unaffected baby. The proportion is likely to rise in the next few years, given that six participants who are yet to experience success are still attempting PGT-M. Genetic susceptibility to cancer was therefore not an obstacle to PGT-M. Patients should, however, be carefully monitored before and during the process, as illustrated by the two incident cancers in our series. In a meta-analysis published after the initial version of this article was submitted, the authors observed PGT-M success rates in patients with hereditary cancer syndromes close to those for other indications [7]. While we could only report overall success rates, the meta-analysis gave clinical pregnancy and live birth rates per cycle with embryo transfer of 40.1% and 33.2, respectively. The rates were lower when HBOC cases were excluded, at 32.7% and 25.5%, respectively.

Age at PGT-M initiation seemed predictive of success, especially for women. Indeed, the mean age was five years younger in the success group compared with patients who had failed to conceive after at least one cycle (27 years old vs. 32). We acknowledge the small number of cases in our study and the impossibility to perform meaningful statistical analyses in this context. This observation is, however, biologically plausible and supported by previous publications [8, 9].

Of the 17 patients who attempted PGT-M, only one had previously received chemotherapy. PGT-M has failed so far in this female *APC* PV heterozygote with a history of colorectal cancer. It is difficult to know whether failure was related to chemotherapy. There are reports in the literature of diminished response to ovulation induction in patients who have previously received systemic cancer treatment [10]. However, stimulation and embryo conception were actually successful in this case, but no embryo was viable in the second cycle (all embryos carried the PV in the first cycle).

Our series is not representative of cancer susceptibility syndromes seen in cancer genetics clinics, even though two of the participating centers had a very diverse patient recruitment. Indeed, the most represented group was VHL followed by FAP, while there was only one patient with HBOC and none with Lynch syndrome. This is to be expected in France, as national guidelines formally consider PGT-

M for syndromes associated with a high and early-onset tumor risk (i.e. children or young adults), a very high lifetime risk, limited screening or risk-reduction possibilities, or severe consequences of risk-reducing surgery [5]. However, it is up to the geneticist to address the issue of PGT-M with patients, as there is no obligation (or even recommendation) for them to do so. The above criteria apply to VHL, FAP, MEN1, Li-Fraumeni, and even hereditary diffuse gastric cancer. However, unlike in countries such as Israel or the Netherlands, PGT-M is usually not considered for syndromes with adult-onset cancer risk, and effective screening modalities and risk-reducing surgery. It can, however, be discussed on a case-by-case basis for very specific situations, depending on the patient's personal and family history. HBOC and Lynch syndrome are, therefore, except in particular circumstances, excluded. This restrictive policy was supported by ART and cancer genetics experts in a 2009 study, although opinions might have changed in the meantime [11].

While our aim is not to change PGT-M practice in France, we believe, like Quinn *et al.* in a 2012 meta-analysis and literature review, that young adults with cancer susceptibility syndromes in general should systematically be informed about PGT-M by their cancer genetics team [12]. Our observation that only half of the participants had been told about PGT-M by their geneticist suggests this is not even the case for those officially eligible for the procedure. Furthermore, comparison of the number of heterozygotes who embarked on a PGT-M procedure with the total number of cases followed in our cancer genetics clinics shows that the proportion is only 9/946 (1%) for VHL and 8/340 (2.4%) for FAP. Finally, the overrepresentation of patients from the "higher managerial, administrative and professional occupations" socio-professional category suggests that education and income facilitate access to medical information and more specifically to PGT-M.

The difficulties highlighted in this paper also appear prevalent in other countries. Among 370 adults in the United States with cancer susceptibility syndromes, only 24% were aware of PGT-M, whereas the vast majority (72%) felt it should be offered when the procedure was explained to them [13]. Even in the Netherlands, where genetics professionals seem very open about ART, making a reproductive choice was reported as (very) difficult by 43% of patients with HBOC who had made a reproductive decision after reproductive counseling, while 69% showed a need for additional support [14].

In conclusion, PGT-M outcomes in patients with cancer susceptibility syndromes were satisfactory. The predominance of cases with syndromes characterized by early-onset, highly penetrant disease is explained by the rather restrictive French guidelines, and PGT-M criteria might need reassessing in the near future.

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LEGENDS

Figure 1: Flowchart