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Case Report

Preimplantation genetic diagnosis for a single gene mutation for succinate dehydrogenase subunit B (the genetic basis for malignant paraganglioma) with successful pregnancy

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Summary

Purpose: To report the first successful case of the birth of normal baby using preimplantation diagnosis for hereditary paraganglioma (PGL) followed by embryo transfer and to emphasize the importance of using mild follicle stimulating hormone (FSH) stimulation for IVF in women with diminished oocyte reserve. *Materials and Methods:* The female partner had a baseline serum FSH of 16.5 mIU/mL and the male partner had the malignant hereditary form of the PGL – pheochromocytoma (PGL/PCC) syndrome related to a mutation of the nuclear mitochondrial enzyme, succinate-dehydrogenase enzyme (specifically the B subunit) (SDHB). He was suffering from the malignant transformation of these neuroendocrine tumors. Before his death, he wanted to enjoy for a short time a baby with his own genes but feared passing the SDHB autosomal gene mutation to their child. *Results:* Eight blastomeres from eight embryos biopsied on day 3 were tested for SDHB gene by polymerase chain reaction. These eight metaphase II oocytes were obtained following mild FSH stimulation (150 units from day 3). Intracytoplasmic sperm injection (ICSI) was performed using the frozen/thawed sperm of this 35-year-old male suffering from a malignant pheochromocytoma. Five of the eight embryos were found to have mutations of the SDHB gene. Two embryos with normal SDHB were transferred and one resulted in a healthy baby. Genetic testing of the baby confirmed the absence of the SDHB mutation. *Discussion:* The successful pregnancy supports, but does not prove, the importance of using mild FSH stimulation in the presence of diminished oocyte reserve to inhibit the iatrogenic development of a much higher percentage of embryos with aneuploidy.

Key words: Malignant hereditary paraganglioma; Pre-implantation diagnosis; Diminished oocyte reserve; Mild ovarian hyperstimulation.

Introduction

Paraganglioma (PGL) and pheochromocytoma (PCC) are neuroendocrine tumors arising from the neural crest cell lineage; the former arise from extra adrenal sites while the latter arise from the adrenal medulla. Although generally benign, PGL and PCC can be malignant, can produce excessive catecholamines, and can compress nearby structures or cause pain, all of which contribute to significant morbidity and mortality.

Previously regarded as predominantly sporadic, recent advances in our understanding of the molecular genetics underlying PGL/PCC suggest that the two entities are frequently associated with any of a growing number of PGL/PCC syndromes (PPS). In the past 15 years, the identification of a dozen susceptibility genes and several putative genes has led to the characterization of distinct PPS with evolving genotype-phenotype correlations [1, 2]. About 35% of apparently sporadic PCC/PGL have a hereditary component [3].

Hereditary PGLs (PGL1-5) are a group of diseases that are associated with the development of PCC and/or PGL (including head and neck PGL, especially the carotid body or the vagus nerve). The genetics of these disorders predominantly involve mutations of the genes encoding for succinate dehydrogenase (SDH) subunits.

The SDH enzyme is an inner mitochondrial membrane enzyme critical to both the tricarboxylic acid cycle and complex 2 of the electron transport chain [3]. The SDH enzyme is made of four subunits (SDHA, SDHB, SDHC, and SDHD). They catalyze the oxidation of succinate to fumarate. Mutations in the SDHB and the SDHD genes have been the most well-characterized of the SDH deficiencies. It is inherited as an autosomal dominant.

Malignancy is reported in two-thirds of SDHB associated tumors and most are in the abdomen [2]. Patients with germline SDH B/C/D mutations are also at risk for the development of an aggressive form of kidney cancer [2].

A case is reported herein where a man dying from ma-

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lignancy associated with the PGL-4 mutation (SDHB) who desperately wanted to have a child with his own genetic characteristics before dying, but a child that was free of this genetic disorder. He thus requested to have in vitro fertilization-embryo transfer with pre-implantation diagnosis (PGD) to exclude the SDHB mutation despite his wife's diminished oocyte reserve.

Case Report

A 35-year-old male and a 36-year-old female presented with primary infertility of three years' duration. The female partner was advised by two previous reproductive endocrinologist/infertility (REI) specialists that she would need donor oocytes because of her serum day 3 follicle stimulating hormone (FSH) of 16.5 mIU/mL. One REI center attempted IVF without PGD using a very high FSH stimulation protocol (600 IU FSH *vs*. 150 IU FSH that we used), and her first cycle was cancelled for insufficient follicles; only one of four oocytes fertilized in cycle 2, none of five oocytes fertilized from cycle 3, and three of ten fertilized in cycle 4 but only one embryo made it to transfer. There was no pregnancy from the two embryos transferred. Her husband had a normal semen analysis but he was dying from malignant transformation of the hereditary PGL syndrome related to being heterozygous for a C to T mutation of nucleotide 136 of the SDHB gene that changes a codon for arginine to a premature stop codon. The previous IVF procedure was performed before his diagnosis of malignant transformation of the PG2 syndrome. He also had a sister with the same syndrome. Several sperm samples were frozen prior to his chemotherapy. They wanted to conceive by IVF-ET with the transfer of embryos that were devoid of this dreaded autosomal dominant mutated gene [PGL-4 (SDHB)] that was the cause of his condition by performing preimplantation genetic diagnosis. They were not interested in options of: 1) donor sperm, 2) donor embryos, 3) conception naturally with 50% odds of a normal conception with termination of pregnancy if chorionic villus sampling and testing for SDHB revealed the almost sure likelihood of developing the PGL syndrome.

There was no precedent in the literature that could be found of PGD used to produce a baby following IVF for a SDHB or any SDH disorder. A probe was created for this particular mutated gene to allow the identification of those embryos that had the SDHB mutation.

Despite diminished oocyte reserve and the use of a mild FSH stimulation protocol, eight embryos reached day 3 when a single blastomere was biopsied on each one and sent for detection of the presence of SDHB mutation. One of his frozen sperm vials was thawed to inseminate the oocyte.

Five of the eight embryos were positive for SDHB mutation. Two normal embryos were transferred resulting in the delivery of one healthy baby. The other embryo was frozen and five embryos with SDHB were discarded by the couple. The baby had genetic testing and is devoid of the SDHB mutation. The father is still alive and is enjoying life with his daughter.

The couple earned only a medium income and her first 3 IVF cycles were covered by insurance but she had to pay out of pocket for the IVF cycle with our group plus the expense of PGD. Nevertheless achieving a pregnancy with his sperm was so important to the couple that they were willing to undergo the expense despite failing 4 times before with IVF.

Discussion

This appears to be the first case report of using PGD to prevent a baby from being born with the PGL/PCC syndrome. There may be other cases either not reported or not published as yet.

Despite many publications that younger women < 39 years with diminished oocyte reserve have almost the same success rate as their age peers with normal oocyte reserve, as long as mild ovarian stimulation is used, there are still many REIs wrongly advising these couples that their oocytes have poor quality and their eggs are of the same quality as 44- to 45-year-old women [4-7].

Though she had only one eight-cell embryo to transfer, one study showed in women aged < 39 years with marked diminished oocyte reserve that the transfer of just one embryo that reaches an eight-cell stage by day 3 results in a 42.4% clinical (viability by ultrasound at eight weeks) pregnancy rate and a 36.4% live delivered pregnancy rate [8].

We believe that the failure to achieve a pregnancy following four attempts at IVF in a previous IVF center was the use of excessive FSH stimulation. Raising the FSH too high in the follicular phase may lead to downregulation of an FSH receptor, which when interacting with FSH, leads to a molecule that is important for proper meiosis II function. Without this key molecule, meiosis II defects occur which produces embryos with aneuploidy, in contrast to meiosis I errors that result from mitochondrial dysfunction of women of advanced reproductive age and generally involves six specific chromosomes and mainly one trisomy per embryo. The meiosis II errors that occur from high dosage FSH in younger women with diminished oocyte reserve or women of advanced reproductive age allows trisomies of many different autosomal chromosomes and frequently more than one in each embryo [5, 7].

The female partner realized that she would have to eventually raise a child by herself, but she stated that she could accept her husband's death easier if she knew that a part of him lives on in her child. Furthermore, she wanted to make her husband as happy as possible for his short time remaining to live. She knew he would enjoy his remaining time with a child known to carry on his genes without the risk of developing the hereditary PGL/PCC syndrome.

References

[1] Rana H.Q., Rainville I.R., Vaidya A.: "Genetic testing in the clinical care of patients with pheochromocytoma and paraganglioma". *Endocrinol.*, 2014, *21*, 166.

[2] Pacak K., Wimalawansa S.J.: "Pheochromocytoma and paraganglioma". *Endocr. Prac.*, 2015, *21*, 406.

[3] Shuch B., Ricketts C.J., Metwalli A.R., Pacak K., Linehan W.M: "The genetic basis of pheochromocytoma and paraganglioma: Implications for management". *Urology*, 2014, *83*, 1225.

[4] Check J.H.: "Physicians should be more open-minded about performing in vitro fertilization-embryo transfer in women with dimin-

ished oocyte reserve and consider the couple's wishes and desires". *Clin. Exp. Obstet. Gynecol.*, 2012, *39*, 5.
[5] Check J.H.: "Optimizing IVF outcomes for women with diminished oocyte reserve". *Expert Rev. Obstet. Gynecol.*, 2013, *8*, 401.
[6] Check J.H., Wilson C.: "The younger the patients the less adverse effect of diminished oocyte reserve on outcome following in vitro fertilization-embryo transfer as long as the proper ovarian stimulation protocol is used". *J. Reprod. Contracep.*, 2013, *24*, 221.
[7] Check J.H.: "Premature ovarian insufficiency – fertility challenge". *Minerva Ginecol.*, 2014, *66*, 133.
[8] Check J.H., Summers-Chase D., Yuan W., Horwath D., Wilson C.: "Effect of embryo quality on pregnancy outcome following single embryo transfer in women with a diminished egg reserve". *Fertil. Steril.*, 2007, *87*, 749.

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