J Assist Reprod Genet (2017) 34:723–724
DOI 10.1007/s10815-017-0907-5

COMMENTARY

Prenatal screening for chromosomal abnormalities in IVF patients that opted for preimplantation genetic screening/diagnosis (PGS/D): a need for revised algorithms in the era of personalized medicine

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Received: 27 December 2016 / Accepted: 7 March 2017 / Published online: 29 March 2017

Abstract Obstetricians offer prenatal screening for most common chromosomal abnormalities to all pregnant women including those that had in vitro fertilization (IVF) and preimplantation genetic screening/diagnosis (PGS/D). We propose that free fetal DNA in maternal circulation together with the second trimester maternal serum alfa feto protein (MSAFP) and ultrasound imaging is the best prenatal screening test for chromosomal abnormalities and congenital anomalies in IVF-PGD/S patients because risk estimations from all other prenatal screening algorithms for chromosomal abnormalities depend heavily on maternal age which is irrelevant in PGS/D patients.

Keywords IVF · Assisted reproductive technologies · Preimplantation genetic screening · Preimplantation genetic diagnosis · Prenatal screening for aneuploidy · Noninvasive prenatal screening

The use of in vitro fertilization (IVF) has steadily increased over the last decades [1]. Recent reports suggest that in the USA, 4–6% of all pregnancies are conceived by IVF with more than 75% of infertility clinics offering preimplantation genetic screening/diagnosis (PGS/D) [2, 3]. This has happened because selecting genetically normal embryos after targeted sampling and testing of polar bodies, blastomeres, or early differentiated trophectoderm cells can avoid the termination of pregnancy for a genetically abnormal fetus [4]. Also because IVF with PGS provides a selection advantage that increases the chance of a live birth on a per embryo transfer basis.

Since PGS/D was introduced during the 1980s, couples at risk for having descendants with a distinct genetic disorders such as Huntington disease, hemophilia, cystic fibrosis, or chromosomal abnormalities due to parental structural chromosomal imbalances have the option of testing their embryo before the initiation of intrauterine development. This can avoid a termination of the pregnancy after prenatal diagnosis or the difficult acceptance of postnatal diagnosis of the disorder [1, 2]. Moreover, over the decades, there have been remarkable advancements in preimplantation techniques that have allowed for very accurate screening for all chromosomal abnormalities. Indeed, molecular diagnostic methods including multiplex PCR, single-nucleotide polymorphism microarray (SNP array), comparative genomic hybridization (aCGH), and next-generation sequencing (NGS) can analyze for numerical abnormalities of all chromosome pairs in preimplantation embryos with the ability to concurrently avoid the potential effect of parental structural chromosomal imbalances; with reports indicating clinical pregnancy rates beyond 60% in patients that had contemporary PGS [4–8].

However, compared to the general obstetrical population, IVF patients with singleton pregnancies are seen in consultation more frequently by the obstetrician. The reasons are (1) IVF patients have close to four times greater risk for low birth weight (29% IVF vs. 8% general population), (2) IVF patients have an increased risk for preterm birth (33.6% for IVF patients compared to 11.4% in the general obstetric population), and (3) existing concern that IVF patients with or without PGS/D have a greater risk for birth defects and genetic abnormalities [1, 2, 8, 9]. It is important to point out that at the moment it is not clear if these epidemiologic observations are distinctive of the patient population requiring IVF or caused by the IVF/PGD/S methods. In addition, because

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PGS/D errors have been reported [10, 11], prenatal diagnosis by ultrasound-guided chorionic villous sampling or amniocentesis should be offered to all IVF-PGS/D patients.

Patients not interested in prenatal diagnosis should have prenatal screening for chromosomal abnormalities and a detailed sonographic evaluation for congenital anomalies. One of the problems for obstetricians managing IVF-PGS/D patients is that prenatal screening tests for chromosomal abnormalities are based on Bayesian analysis in which the maternal age-related risk is the a priori risk that will be modified by the results of a combination of maternal serum and sonographic biomarkers evaluated at defined gestational age windows [12]. These screening algorithms do not take into consideration that the embryo was selected using PGD/S causing confusion, emotional distress in the patient, and final estimations of risk for chromosomal abnormalities that are not accurate. We propose using only the analysis of free fetal DNA (*f*FDNA) in maternal circulation together with the second trimester maternal serum alfa feto protein (MSAFP) and the first and second trimester ultrasound imaging for prenatal aneuploidy and congenital anomalies screening [13–15] in IVF-PGS/D patients until commercial laboratories that depend on maternal serum biomarkers report risks for chromosomal abnormalities adjusted for the a priori use of the alternative PGD/S choices.

The advantage of the analysis of *f*FDNA is that the report is easier to interpret and explain to the patient since there is a simmilar a - posteriori numerical risk for the chromosomal abnormalities tested for all patients. The drawback of using *f*FDNA screening in IVF-PGS/D patients is that obstetricians will miss the information for adverse obstetric, perinatal, and fetal outcomes provided by the abnormal concentration of the maternal serum biomarkers [16]. For this reason, we encourage commercial laboratories that use maternal serum biomarkers to screening for chromosomal abnormalities and adverse pregnancy outcomes to integrate PGS/D in their algorithms in this era of personalized medicine.

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