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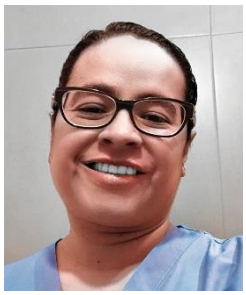
Importance of pre-test genetic counselling in couples undergoing assisted reproductive techniques (ART) and preimplantation genetic testing (PGT).



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ABSTRACT

Seven embryo biopsies from a 33 female and 39 male year-old couple were sent for PGD, all resulted in aneuploid embryos. When analysing the case, we notice that the male had a previous 15-year-old daughter and several semen analyses with fluctuating teratozoospermia from 29% to 100%. Although ICSI and PGD are powerful tools in male factor infertility, it is not recommended in all cases, especially the ones that may be due to reversible causes. Male infertility should be evaluated thoroughly and accompanied by proper genetic studies and genetic counselling so that the couple is offered options suitable for their medical conditions and economy.

KEYWORDS: Genetic counselling, preimplantation genetic diagnosis, assisted reproductive techniques.

MANUSCRIPT

Seven embryo biopsies were sent to us for Preimplantation Genetic Diagnosis (PGD), the clinical notes included ages: female 33 and male 39 years, a masculine factor not specified was pointed out. Most embryos were biopsied on day 3 whereas the last one was biopsied on day 6. Embryo morphology classification was ambiguous and all were aneuploid, as seen in Table 1. About a month later the medical staff at the clinic asked us to reach out to the couple as they were having several doubts about their results. However, the clinical panorama was entirely different from the one referred to us on the paperwork. The first six embryos were from an ovum donor and the last one was from the female, this was not disclosed in the written forms and it is of course, relevant for counselling purposes. The other point of interest is that the male has a previous healthy daughter 15 years old, and has several semen analyses, with fluctuating teratozoospermia from 29% to 100%, Table 2.

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EMBRYO	DAY	MORPHOLOGY CLASSIFICATION	ISCN FORMULA	DIAGNOSIS
(7)	3	8	Complex Aneuploidy	Aneuploid embryo
(9)	3	8	sseq(18)x3^{+}	Aneuploid female
(10)	3	7	sseq(13)x3,(21)x1	Aneuploid male
(11)	3	8	sseq(2,12,21p)x3,(20)x1 mos	Aneuploid female
(12)	3	6	Complex Aneuploidy	Aneuploid embryo
(13)	3	6	Complex Aneuploidy	Aneuploid embryo
(19)	6	BH	sseq(Xp,Xq,21)x3^{+}	Aneuploid female

Table 1

ITEM/DATE	03/2016	03/03/2020	03/14/2020	04/2020	05/2022	Normal value
Volume	6ml	5.1ml	0.5ml	5.8ml	4.5	>1.5ml
pH	6	7.5	9	9	9	7.5
Concentration	93mill/ml	12mill/ml	225mill/ml	53mill/ml	120mill/mil	>15mill/ml
A	NA	0	0	0	0	NA
B	NA	23	45	42	63	NA
C	NA	44	30	14	24	NA
D	NA	33	45	44	14	NA
A+B	NA	23	NA	42	86	NA
Normal morph	71	0	3	96	3	>4%
Abnormal	29	100	97	4	97	NA
Head	NA	67	100	84.3	60.4	NA
Body	NA	40	63.9	78.1	93.8	NA
Tail	NA	23	42.2	8.3	19.5	NA

Table 2

Although sperms with abnormal morphology have been used for intracytoplasmic sperm injection (ICSI) successfully, several studies show that high rates of disomy and diploidy are related to severe teratozoospermia and therefore ICSI is not recommended in these cases[(1)]. A study performed by Kahraman in 2004 with macrocephalic spermatozoa showed that the quality of spermatozoa is indeed correlated to fertilisation and consequently with embryo development. It is proposed that a sperm-derived oocyte activation factor in abnormal spermatozoa may lead to an abortive oocyte activation and subsequently failure of pronuclear development[(1)]. Also, the configuration of the centrosome and aster formation which is critical in the development of the zygote may be defective in morphologically abnormal sperm[(1)]. Increased incidence of chromosomal abnormalities correlates with decreased semen quality as well as decreased pregnancy outcomes, and though there is not a standardized technique in sperm selection to discard chromosomal abnormalities and preserve the function for ICSI[(2)], sperm with morphological abnormalities should be discarded. However, other studies suggest that oligospermia and/or teratozoospermia do not appear to be associated with increased embryo aneuploidy but do correlate with poorer fertilization rates and embryo implantation[(3)]. Absolute teratozoospermia associated with sperm chromosomal abnormalities is well documented to be associated to a high rate of chromosomal abnormalities on preimplantation embryos, cycle cancellations, abortion as well as low fertilization, implantation and clinical pregnancy rates; though other forms of sperm chromosomal abnormalities and assisted reproduction failure should be studied further and though the selection of normal sperm for ICSI does not eliminate the chance of chromosomal abnormality in the infertile man[(2)], it does reduce the risk in a male with previous fertility proven, as our patient. Severe and/or absolute teratozoospermia in recent studies has been linked to

a three-fold and up to a 4.4 fold higher rate of sex aneuploidies in their embryos[4, 5]. Whereas there is controversy if, in fact, abnormal morphology is related to increased aneuploidy rate, some studies indicate that sperm morphology does not reflect chromosomal endowment and that ICSI is a suitable choice even if there is not even one normal sperm[4]; other studies have shown that patients with severe teratozoospermia (normal forms <10%) have a significantly higher aneuploidy rate in comparison with patients with a lower degree of teratozoospermia[6] as well as a higher risk of diploidy and polyploidy (Rodrigo). There is also a correlation between oligospermia and higher rates of teratozoospermia, as a checkpoint in meiosis leads to an arrest of abnormal cells[4,5]. The incidence of males with abnormal sperm morphology and increased rate of aneuploidies detected by FISH in sperm is higher in nonobstructive causes[5].

Patients with oligoasthenoteratozoospermia have synaptic chromosomal anomalies that are restricted to the germ cell line up to 26.7%, and between 8-12% of abortions with trisomies 13, 18, and 21 are linked to paternal origin[1,5] revealing the important role of sperm morphology to the proper development of the zygote. In the study conducted by Kahraman in 2006, no benefits from PGD were observed in the group of patients with zero normal morphology group[2] which gave the rationale of this paper: if the couple agreed to have ovum donation, sperm donation should have been offered as well, considering that with a high degree of abnormal sperm in the male, the chance of having aneuploid embryos was high, and the investment in the medical process was not worthy. It is important to underline that patients with severe teratozoospermia such as the male patient in this case who undergo ICSI, can display a higher rate of sex chromosome aneuploidies in their embryos, in comparison to moderate teratozoospermia[4]. Besides, the need for adequate diagnosis and treatment in the male should be considered, as some of the causes may be reversible. It is important that medical staff consider the well-being and economy of the couple regarding their decisions and health issues that may be not necessarily related to the reason for consultation. Directive consultation and adequate counselling are two different things and our role is to guide the patient in all possible outcomes that may be related to their health. The main objective of PGD is to diminish the probability of an early miscarriage (due to chromosomal abnormalities) and the emotional and economic impact that this event inflicts on the couples, therefore if there is by any chance augmented possibilities of not having a single euploid embryo due to previously known medical conditions, couples should be offered all available alternatives.

Male infertility has been a recurrent topic in recent studies, it is estimated that approximately 30 million men are infertile[4]. ICSI and PGD are powerful and helpful tools, ISCI reduces the requirements of semen quality samples, specifically for motility[4]; however we suggest in the cases of proven previous male fertility, as in this couple, reversible causes of teratozoospermia should be corrected or intended to correct before offering whichever assisted reproductive technology. In fact, recent studies show genomic abnormalities that lead to specific abnormal forms of the sperm, some of which are contraindications for ICSI, for example, AURKC mutations which lead to a higher risk of aneuploidy; or in all patients with globozoospermia due to an oocyte activation anomaly[7].

CONCLUSION

The approach to male fertility should be changed, though spermatobioscopy has been and is still a great tool, it is not a final answer, and more specific studies should be offered to patients to optimize treatment and reproductive strategies.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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