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Research Article

Prospective Application of Preimplantation Genetic Testing (Pgt) for Primary Prevention of Hereditary Deafness

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Abstract:

Background: Premature progesterone elevation (PE) on the day of human chorionic gonadotropin (hCG) trigger during controlled ovarian stimulation has been reported in IVF/ICSI cycles despite the use of GnRH agonist or antagonist protocols. The impact of elevated progesterone levels on reproductive outcomes remains controversial, particularly regarding implantation and clinical pregnancy rates. Identifying clinically relevant progesterone thresholds may improve treatment strategies and optimize IVF/ICSI outcomes.

Objective: To evaluate the relationship between serum progesterone levels on the day of hCG trigger and reproductive outcomes in IVF/ICSI cycles and to determine the progesterone threshold associated with adverse clinical outcomes.

Methods: This prospective cohort study included 95 infertile women aged 20–35 years undergoing IVF/ICSI treatment at Ain Shams University Hospital between June 2023 and October 2024. Participants were categorized according to trigger-day serum progesterone levels into three groups: <1.3 ng/mL, 1.3–1.5 ng/mL, and >1.5 ng/mL. Demographic characteristics, hormonal profiles, ovarian response parameters, fertilization rate, implantation rate, and clinical pregnancy outcomes were compared. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive value of serum progesterone for pregnancy outcomes.

Results: Among the participants, 83.2% had progesterone levels <1.3 ng/mL, 4.2% had levels between 1.3 and 1.5 ng/mL, and 12.6% had levels >1.5 ng/mL. Clinical pregnancy rates were 43.0%, 50.0%, and 25.0%, respectively. Although differences in implantation and pregnancy rates did not reach statistical significance, outcomes were consistently lower in women with progesterone levels >1.5 ng/mL. No significant differences were observed in oocyte yield, embryo quality, fertilization rate, or baseline hormonal parameters. ROC analysis identified a progesterone cutoff value >0.7 ng/mL for predicting pregnancy outcomes (AUC = 0.622, sensitivity = 66.7%, specificity = 64.3%).

Conclusions: Elevated serum progesterone on the day of hCG trigger, particularly levels >1.5 ng/mL, is associated with reduced implantation and clinical pregnancy outcomes in IVF/ICSI cycles. Careful monitoring of progesterone levels and individualized treatment approaches, including consideration of freeze-all strategies, may improve reproductive success.

Keywords: preimplantation genetic testing for monogenic disorders (pgt-m); hereditary deafness (hd); expanded carrier screening (ecs); prospective application of pgt-m

Introduction

Genetic factors account for over half of deafness in children, with a high prevalence in different parts of the world [1-3]. More than 130 genes were described in association with hereditary deafness (HD) (https://hereditaryhearingloss.org/), involving different mode of inheritance.

Although HD is a non-lethal correctable condition, lifelong restoration of hearing cannot match natural hearing, not mentioning a real financial burden. Prenatal diagnosis of HD is possible but leads to a difficult decision of a possible termination of affected pregnancy with a non-lethal correctable condition. Preimplantation genetic testing (PGT) for HD, based on pre-selection for transfer of only unaffected embryos, avoids the risk for pregnancy termination, and most importantly, allows having children without HD [4-7].

Initially applied for avoiding recurrence risk of having severe genetic conditions, PGT-M was applied for those at-risk couples who have already had an affected child with monogenic disorders, However, with introduction of different screening program [8], it has become possible to apply PGT-M for patients without affected family members. We have previously reported our provisional data on the possible shift to prospective application of PGT for HD [9]. Having collected more data on this novel PGT approach, this paper will evaluate the impact of such ascertainment on prospective application of PGT-M for primary prevention of HD.

Materials and Methods

A series of 408 PGT cycles was performed for patients at risk for producing a progeny with HD, which is caused by over 300 mutations in more than dozen different genes mutations.

PGT-M was performed using a standard IVF protocol, coupled with embryo biopsy, with the details described elsewhere [10]. The procedure involves whole genome amplification (WGA) of embryo samples obtained by blastocyst biopsy, followed by multiplex nested PCR analysis of the mutations in question, and closely linked genetic markers in a multiplex heminested system. For each family, heterozygous alleles and haplotypes not shared by parents were selected. This allows detecting and avoiding misdiagnosis due to preferential amplification and allele dropout (ADO), and a possible aneuploidy or uniparental disomy of chromosomes in which the tested mutations are located, that may affect diagnostic accuracy of PGT-M.

For PGT-M cycles, involving an advanced reproductive age of the maternal partner, a combined aneuploidy testing was performed for 24-chromosome aneuploidy testing using a NGS platform with commercially available kit VeriSeq™ PGT Kit (Illumina Inc).

Results and Discussion

In 408 PGT cycles for HD, 449 unaffected embryos were identified for transfer in 395 PGT cycles, yielding 256 (65.0%) clinical pregnancies and birth of 230 children free of HD (Table 1). As can be seen from Table 1, in most PGT-M cycles, HD was caused by mutations in three major genes, GJB2, SLC26A4 and USH2A. These cycles were performed mainly for couples yet without affected children in their family, ascertained through expanded carrier screening. As previously demonstrated (8), in most couples, PGT cycles were performed prospectively with no affected relative in family, with dynamics of referrals for PGT-M steadily increasing in our experience during for than a decade. Figure 1 shows dynamics of prospective PGT for HH during the last twenty years in our experience.

Disease	Gene	# of Cycles	# of transfers	# of embryos transferred	Pregnancy	# of Babies
AURICULOCONDYLAR SYNDROME 2; ARCND2	PLCB4	3	3	5	2	1
DEAFNESS, AUTOSOMAL DOMINANT 3B; DFNA3B	GJB6	2	2	3	1	1
DEAFNESS, AUTOSOMAL RECESSIVE 3; DFNB3	MYO15A	6	5	5	2	2
DEAFNESS, AUTOSOMAL RECESSIVE 8; DFNB8	TMPRSS3	3	3	3	3	2
DEAFNESS, NEUROSENSORY, AUTOSOMAL RECESSIVE 1; DFNB1	GJB2	324	314	353	208	190
DEAFNESS, X-LINKED 1; DFNX1	PRPS1	1	1	1	1	1
PENDRED SYNDROME; PDS	SLC26A4	10	10	9	4	4
USHER SYNDROME, TYPE I; USH1	MYO7A	4	4	4	2	2
USHER SYNDROME, TYPE IF; USH1F	PCDH15	8	5	7	4	2
USHER SYNDROME, TYPE IIA; USH2A	USH2A	36	38	46	22	19
USHER SYNDROME, TYPE IIC; USH2C	ADGRV1	2	2	3	1	1
WAARDENBURG SYNDROME, TYPE 2A; WS2A	MITF	7	7	9	5	4
WOLFRAM SYNDROME 1; WFS1	WFS1	2	1	1	1	1
TOTAL		408	395	449	256	230

Table 1: PGT for Hereditary Deafness

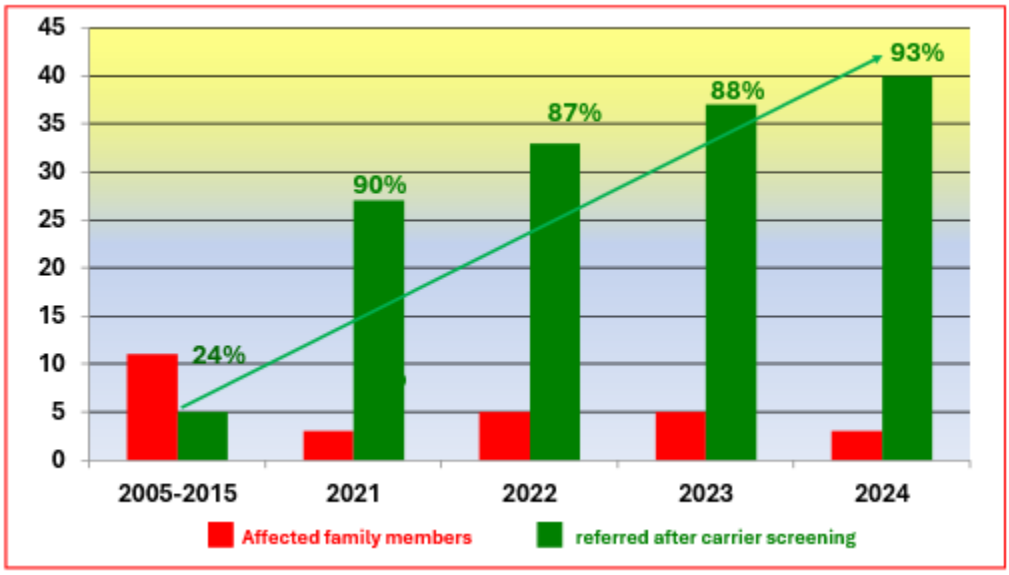

Figure 1: Increase in PGT-M for Hereditary deafness (GJB2 gene) after I introduction of carrier screening

A low treatment efficiency for therapeutic interventions and high (25% - 50%) risks of recurrence in each pregnancy for genetic disorders makes PGT-M highly relevant for the purpose of primary prevention of genetic disease. However, at-risk couples usually do not know about their at-risk status until they have an affected child, so a sufficient reduction of the affected birth prevalence cannot be achieved in the absence of screening programs.

It is of interest that significant increase in PGT-M is observed also for conditions, which originally have not even been an indication for PGT-M. Such an increase is clearly due to the introduction of ECS programs, which allow at-risk couples to avoid even the first occurrence of disease. So PGT-M is no longer applied to prevent a recurrence after couples have had an affected offspring or had a relative with these conditions but has also been performed prospectively for couples with no affected offspring, detected through screening programs, previously offered exclusively for special ethnic groups or selected genetic conditions. ECS and targeted gene panels will increase the number of genetic disorders amenable to PGT-M prospectively, representing a real form of primary prevention, as it allows avoiding affected pregnancies, and establishing unaffected pregnancies from the onset. Thus, presented dynamics of PGT-M for HD demonstrates the shift from retrospective to prospective application of PGT-M performed for couples with no affected relative, with the number of prospective PGT-M cases more than doubled in the last decade [9]. This may lead to the application PGT-M beyond family level, allowing to offer PGT-M prospectively before the birth of an affected child, as a tool for primary prevention of genetic disorders.

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