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Research Article

A Call for Increasing Capacity of PGT Services in Saudi Arabia: A Retrospective Study For the Accessibility To PGT

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ABSTRACT

Objectives: To assess the demographic characteristics and outcomes of couples undergoing Pre-Implantation Genetic Testing (PGT) at King Faisal Specialist Hospital and Research Center (KFSH and RC) in Riyadh, Saudi Arabia.

Methods: For this retrospective study, information was extracted from the hospital electronic database and *In-Vitro* Fertilization (IVF) unit medical records.

Results: The number of couples with known genetic mutations participating in the *In-Vitro* Fertilization-Preimplantation Genetic Testing (IVF-PGT) treatment process over the period of 2018 to 2020 was 1,454. The mean and Standard Deviation (SD) of age was 33.3 (4.9). The majority of the patients (35%) belonged to the 31-35-year-old age group, followed by the 18-30-year-old age group, accounting for 28%. The study also analyzed the number of healthy children, (those not affected by genetic diseases). The results showed that 59% of couples had only 1 normal child, 33% of couples had 2 normal children, and only 11% of couples had 3 or more normal children. The average waiting time for IVF-PGT treatment cycles was 15.4 months. Among all participants in the study, 5% of them have a baby from the previous PGT cycle. Following their treatment during the study period, the age group of 21-25 years old had the highest age-specific live birth rates (28%), and women over 40 years old had the lowest rates (2.5%).

Conclusion: We concluded that there is an urgent need to improve the capacity of PGT services in Saudi Arabia to reduce waiting time and to avoid delays in treatment that negatively affect live births and the success rate of PGT.

Keywords: Pre-implantation genetic diagnosis; IVF-PGT treatment; Live birth rates

INTRODUCTION

In Saudi Arabia, genetic disorders are common due to consanguineous marriages and more genetic mutations are discovered with the application of next-generation sequencing [1]. The high prevalence rate can be accrued from high consanguinity since consanguineous marriages account for 56 per cent of marriages in the Middle East and Saudi Arabia [2]. The ability of couples with established genetic abnormalities to have healthy children opens up new horizons in reproductive medicine. Pre-implantation Genetic Testing (PGT) is an established procedure involving a genetic analysis of embryonic cells and unaffected embryo transfer into the uterus.

It was first performed by Handyside, et al. [3] in 1990. King Faisal Specialist Hospital and Research Center in Riyadh was the first centre to provide PGT services in Saudi Arabia since 2001 [4].

With the improvement of the genetic diagnosis and increased family and provider awareness, the new family referrals to the PGT program at KFSH RC have tripled in 2018 compared to 2014, from 169 new families in 2014, to 663 new families in 2018 for single or double or triple gene disorders. IVF-PGT treatment cycles can be performed more than once depending on the success rate and the couple's desire for a certain number of healthy children in their family planning. Therefore, understanding the patient population interested in this treatment while planning for the utilization of the resources becomes crucial to the service provider.

Currently, the number of IVF PGT cycles performed for single gene disorder has increased from 200 cycles per annum in 2017 to more than 400 IVF PGT cycles annually in King Faisal Specialist Hospital and Research Center. Nonetheless, this does not meet the demand of the current patients and new PGT referrals to the unit. The IVF PGT program's success rate is linked directly

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to the female partner age, thus waiting time and delays in service provision will have negative medical and psychological impacts on these families [5-7]. Therefore, every year, delaying access to PGT minimizes the chances of IVF PGT success. Some European countries including Italy, Switzerland, France, and the United Kingdom have established policies that regulate the use of PGT including the conditions which can be tested and several cycles that can be offered [8].

In this retrospective study, we assessed the demographic characteristics and outcomes of couples seeking pre-implantation genetic testing at King Faisal Specialist Hospital and Research Center in Riyadh. Various information was obtained from the patient's files regarding female age, the number of their normal, affected and dead children, the number of PGT cycles they underwent, along with the outcomes, and the exact time each patient waited before starting an IVF-PGT cycle. Understanding this information can help the policymakers in planning for the services and help in optimizing patients access to genetic disease prevention.

SUBJECTS AND METHODS

In our program, the classical process was that patients are seen in the clinics, and options for genetic preventions and procedures were explained. Once they agree to PGT, the routine IVF investigations were performed and were asked to call to start IVF PGT treatment. When the number of the referrals was limited at the beginning of the program this was a reasonable solution to satisfy the demands., The study included couples who were called to start IVF-PGT treatment according to our process at KFSH and RC in Riyadh from January 2018 to December 2020. The data of the patients were extracted from the electronic database of the hospital and the medical records of the IVF unit. Patients with cryopreserved IVF cycles or patients who were lost to follow-up for IVF cycles were excluded from the study. The demographic data obtained includes the female patient's age, the number of normal, affected, and dead children, the number of PGT cycles performed on the patient, including the outcome, and the exact time each patient waited before starting an IVF-PGT cycle. The local IRB approval was obtained.

STATISTICAL ANALYSIS

Continuous variables were expressed as the standard deviation of the mean. All analyses were performed using Windows Statistical Science and Social Statistics Software Package Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, the total number of patients who met the eligibility criteria and were included in this study was 1,454. The age of the patients ranged between 18 to 44 years old, and the mean age was 33.3 ± 4.9 years. The majority of the patients (35%) belonged to the 31-35-year-old age group, followed by the 18-30-year-old age group, accounting for 28%. The age group from 36 to 38 years old accounted for 21%; 10% for the age group of 39-40 years old, and the smallest percentage was 6% for the age group of 41-44 years old (Figure 1).

In 59% of families, the number of normal, (genetically unaffected) children per patient were only 1 normal child or less, 28% of families had 2 normal children, and only 11% of families had 3 or more normal children.

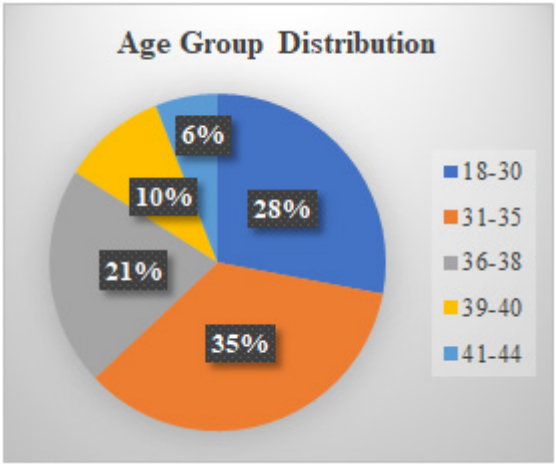

Figure 1: Age Group Distribution.

Table 1: Age Group Distribution.

Age (mean+SD)	33.3 (4.9)
Median age	33
Have 1 normal child	58%
Have 2 normal children	27%
Have 3 normal children	11%
Have 1 child from PGD	4%
Have 2 children from PGD	1%
1 PGD cycle	24%
2 PGD cycles	11%
3 or more PGD cycles	3%
Average waiting time by months (SD)	15.3 (4.7)

A total of 553 out of 1,454 patients had undergone previous IVF-PGT cycles (38%) at KFSH and RC. Among those, 24% of patients had only 1 PGT cycle, 11% of patients had 2 PGT cycles, and 3% of patients had 3 or more PGT cycles (Table 1).

Among the participants, only 5% (73 cases) of the samples were found to have babies from previous PGT cycles, 4% of them (58 cases) had 1 PGT child, and 1% (15 cases) had 2 or more PGT children.

The average waiting time for IVF-PGT treatment cycles was found to be 15.4 months.

Calculation of live birth rates by age group showed the highest rates in the 21-24-year-old age group, at 29%, followed by 27% in the 26-30-year-old age group. Both age groups of 31-34 and those below the age of 21 years achieved 23% live birth rates. The live birth rates for the age groups 36-38, 39-40, and over 41 years old accounted for 15%, 8%, and 2.5%, respectively (Figure 2).

The percentage of patients with 2 normal children (without the genetic disorder) was calculated by age group, the lowest percentage (12%) was at age of 29 years and below, and the highest percentage (58%) was at age around 39 years old (Figure 3).

DISCUSSION

Pre-Implantation Genetic Diagnosis (PGD) is a form of prenatal diagnosis of early embryos obtained through *In Vitro* Fertilization (IVF). The first successful use of PGD in humans was in 1990 when the British embryologist and geneticist professor Alan Handyside

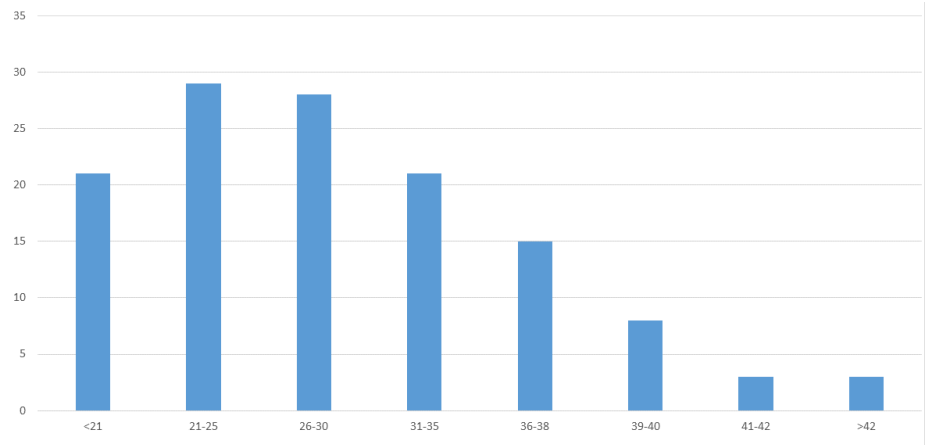

Figure 2: Age-Specific live birth rates.

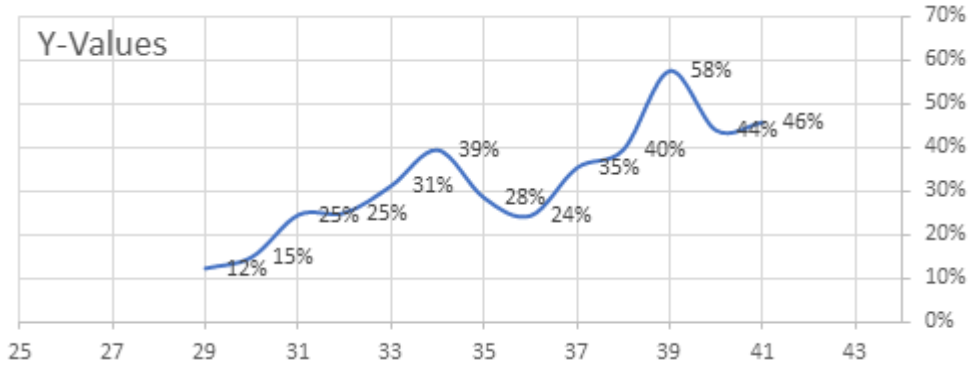

Figure 3: Percentage of Patients who have 2 more normal children distributed.

and his colleagues performed sexing of embryos using Polymerase Chain Reaction (PCR) for the presence of the Y chromosome sequence to avoid males being affected with X-linked adrenal dystrophy and X-linked mental retardation [3]. Shortly thereafter, it was reported that successful PGD has been used for cystic fibrosis, alpha-1 antitrypsin deficiency, and many other disorders of a single gene.

Pre-implantation genetic testing can enable couples at high risk of genetic diseases to have a healthy, genetically related child. After *in vitro* fertilization, the polar bodies or embryonic cells are tested to diagnose certain diseases, and those without the disease are selected for implantation, thereby avoiding the spread of genetic diseases and preventing the complications such as health problems and the psychological burdens that may result from the termination of a pregnancy.

In this article, we studied the couples who were interested to start IVF-PGT treatment cycles at King Faisal Specialist Hospital and Research Center (KFSH and RC) over the period of 2018 to 2020, using predictive values such as the age of the female, the number of normal, affected and dead children, the number of PGT cycles and the number of live births resulting from the PGT intervention in our institute.

As we can see in this paper, the number of couples who are interested to start one cycle is higher than the capacity of the IVF PGT clinic in KFSH and RC. This number included couples who never started any treatment cycle, couples who had failed cycles in the past and would like to have another cycle, or couples who had a successful cycle and healthy child and would now like to have another one. This picture, with the increasing number of new referrals and limited capacity of the unit, is clearly showing that the clinic's inability to provide acceptable services to these families.

Approximately one-third (35%) of the patients waiting to start is above 36 years old and the maximum live birth is 15% after this age. This rate lowered by 50% to 8% between 39-40 years old, and 2.5% when over 41 years. This time-related reduction in the live births rate is expected biologically, making the treatment for those patients a priority.

We also studied the number of healthy children (children not affected by genetic diseases). In the majority of families (59%), the number of normal (genetically unaffected) children per patient was only 1 normal child or none; 28% of families have 2 normal children, and only 11% of families have 3 or more normal children.

According to the live birth rates (25% per cycle) and the waiting time for IVF-PGT cycle (15.4 months), each patient needs an average of 2 IVF-PGT cycles and around 4 years to give birth to a healthy child from PGT.

There are no national guidelines for PGT in Saudi Arabia. In different countries such as the United Kingdom, France, Switzerland, and Italy, the number of patients for PGT (number of cycles per patient) in these countries is restricted by laws, and according to different aspects such as female age, genetic conditions that can be tested, and number of IVF cycles allowed depending on the governmental funding [9]. For this reason, only 38% of the samples (553 patients) had a PGT cycle in our institute, which means that 62% of patients are still waiting for their first PGT cycle, 24% of patients had one PGT cycle, and 11% of patients had two PGT cycles.

The average waiting time was found to be 15.4 months because the IVF unit was only able to perform 200 cycles per year. Although it is increased now to more than 400 PGT cycles per year, the unit is still unable to meet the existing or increasing demands of more than 600 new referral requests every year. This is expected to increase with time unless certain measures are taken to further expand the capacity and regulate the beneficiary with limited resources. Priority needs to be given to patients who will benefit most from IVF PGT (healthy child live birth as outcome) and those who are in the most need (number of living healthy children).

Based on the data of this study and the current situation in KFSHRC IVF PGT services, as we are the only public provider, we wish to propose the following recommendation:

- Expanding the services to meet the demand
- Identifying the population who will benefit most from IVF PGT services to direct the resources to them.
- Identifying the patients who are most in need, for example: having no healthy living children

CONCLUSION

As KFSHRC is the only public hospital currently providing IVF PGT services, this is still limited in Saudi Arabia. We concluded that there is an urgent need to improve and expand Saudi Arabia's PGT service capacity and to apply the policies and regulations which can improve the service by reducing the waiting time and providing more PGT cycles to avoid delays in treatment which has a negative impact on live births and successful treatment of PGT.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest None declared.

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