Journal of Fertilization: In Vitro-IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biol

OPEN ACCESS Freely available online

Research Article

Preimplantation Genetic Diagnosis in Midwest of Brazil

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ABSTRACT

Introduction: With the development of new technologies, Preimplantation Genetic Diagnosis (PGD) performed dramatically increases the ability to detect embryonic and fetal genetic lesions and, as a consequence, substantially improve the selection of embryos for in vitro fertilization.

Objective: To define the most common indications for carrying out the preimplantation genetic study and also to establish the maternal age that presented the most changes and to evaluate the most common results found in the preimplantation genetic study.

Methods: This is a descriptive, cross-sectional, and retrospective study conducted at the Fertile and Humana reproduction clinics, in Goiania, in patients undergoing preimplantation genetic study in assisted reproduction. All patients who underwent the preimplantation genetic study between January 2014 and March 2019 included. The total number was 70 patients, with 101 assisted reproduction cycles.

Results: 101 assisted reproduction cycles were evaluated, with 70 patients. 327 embryos were resulting in 105 normal embryos and 182 altered ones, 40 embryos failed to amplify. Among these 105, 49 transfers were made with 52 transferred embryos. The average maternal age was 36.86 years and the paternal age was 39.20 years. The patients had 7 indications for carrying out the embryo genetic study and 14 of the 70 patients had more than one indication for carrying out the embryo evaluation. The rate of ongoing pregnancy in patients undergoing the genetic study was 34.69%. The main changes found were aneuploidies 86.92%, followed by structural changes 13.18%, linked to gene diseases represented 4.39%. Regarding aneuploidies, embryos with 1 single altered chromosome represented 40.10%, with 2 altered chromosomes, it was 13.10%, with changes in 3 chromosomes, and it was 13.10%. Embryos with 4 or more altered chromosomes were classified as complexes representing 19.70%. Trisomy 16 was the most frequent alteration. Chromosome 22 showed the most changes.

Conclusion: The most common indications were maternal age, screening for aneuploidies and implantation failure. The rate of abnormal embryos increases significantly in the group of patients aged 40 years and over. The main changes found were aneuploidies 82.41%, followed by structural changes 13.18%, linked to gene diseases, representing 4.39%. Among aneuploidies, there was a higher prevalence of trisomy 16, followed by trisomy 15, monosomy X and monosomy 22.

Keywords: Prenatal genetic testing; Infertility; Non-invasive prenatal screening reproductive genetics; Assisted reproductive treatment

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Received: 31-May-2023, Manuscript No. JFIV-22-15052; **Editor assigned:** 02-Jun-2023; PreQc No. JFIV-22-15052 (PQ); **Reviewed:** 16-Jun-2023, Qc No. JFIV-22-15052; **Revised:** 23-Jun-2023, Manuscript No. JFIV-22-15052 (R); **Published:** 30-Jun-2023, DOI: 10.35248/2375-4508.23.11.323

Citation: Saidah TK, Amaral WND, Saidah CM, Evangelista P, Saidah MK, Saidah K (2023) Preimplantation Genetic Diagnosis in Midwest of Brazil. J Fertil *In vitro* IVF Worldw Reprod Med Genet Stem Cell Biol. 11.323

INTRODUCTION

Preimplantation development comprises the early stages of mammalian development before the embryo implanted in the mother's womb. Under normal conditions, after fertilization, the embryo grows until it reaches the blastocyst stage. The blastocyst grows as the cells divide and the cavity expands until it reaches the uterus, where it "hatches" from the pellucid zone to implant in the uterine wall. However, the quality and viability of the embryo can be affected by chromosomal abnormalities, most of which occur during gametogenesis and early embryo development; human embryos produced *in vitro* are especially vulnerable. With the development of new technologies, Prenatal Genetic Testing (PGD) has become a reality, dramatically increasing the ability to detect embryonic and fetal genetic lesions and as a consequence, substantially improved the selection of embryos for *In Vitro* Fertilization (IVF). However, it is still being debated about the practicality and diagnostic accuracy of PGD, due to the concern with invasive biopsy and the potential mosaicism of embryos [1].

The data suggest that PGD significantly reduces the risk of spontaneous abortions in women undergoing *in vitro* fertilization, particularly in women over 40 years of age, and also reduces the risk of trisomy children. Therefore, the objectives of this study are to define the most common indications for carrying out the preimplantation genetic study, to establish the maternal age that showed the most changes and to evaluate the most common results found in the preimplantation genetic study [2].

METHODOLOGY

This study is a descriptive, cross-sectional and retrospective study carried out at the Fertile and Humana reproduction clinics, in Goiania, Midwest of Brazil, in patients submitted to the preimplantation genetic study in assisted reproduction. All patients who underwent the preimplantation genetic study between January 2014 and March 2019 were included.

The total number was 70 patients, with 101 assisted reproduction cycles. The study was approved by the CAEE Research Ethics Committee: 58187916.0.0000.8058. The data entered and in Excel for later treatment of the data using the Windows Statistical Package for Social Science (SPSS) program (version 21.0).

Categorical variables were presented as an absolute value (f) and a percentage value (%).

The Fisher test was used to verify the existence or not of a significant difference between the total numbers of embryos, compared to normal and altered ones, in different age groups [3].

The Mann-Whitney test was used to compare the median of embryos per patient in relation to age groups. The 95% confidence interval was used, that is, $p < 0.05$ was considered significant [4].

RESULTS

101 cycles of assisted reproduction were evaluated, with 70 patients. 327 embryos were resulting in 105 normal and 182 altered, and 40 had amplification failure. Among these 105, 49 transfers were made with 52 transferred embryos. The average maternal age was 36.86 years, and the paternal age was 39.20 years . Table 1 presents the distribution of PGD cases, according to the clinic indication. The patients had 7 for carrying out the embryo genetic study and 14 of the 70 patients had more than one indication for carrying out the embryonic evaluation. The main indication was maternal age with 40%, the second most frequent indication was aneuploidy screening 12.85%; the third most frequent indication was for the deployment failed 8.57%. Table 2 presents the istribution of PGD cases, according to the ongoing pregnancy. The rate of ongoing pregnancy in patients undergoing the genetic study was 34.69%. Table 3 present de distribution of PGD cases, comparing age range and the quality of embryos. The group A had 50.65% of altered embryos, the group B had 52.04%, and the group C had 70.12%. Comparing group A with B there was no difference of altered embryos (p=0.101). Comparing group A with group C the number was altered embryos was (50.65% *vs.* 70.12%, p=0.002). Table 4 present the cases of PGD, according to the number of embryos per patient and age group. In the group A the median was 5, 00 (4, 3-6, 6), the group B the median of embryo per patient was 5.0 (3, 8-6, 5). The group C the median was 2.0 (2, 1-4, 6). The median of embryos per patient between A and C groups was (5.0 *vs.* 2.0, respectively, p=0.009).

Table1: Distribution of PGD cases, according to the clinical indication, Goiânia, Goiás, 2014-2019.

Recommendation	Absolute number (n)	Relative number (%)
Maternal Age	28	40%
Aneuploidy Screening	9	12,85%
Deployment failed	6	8,57%
Sexing	4	5,71%
Repeat abortion	4	5,71%
Genetic Disease	3	4,28%
Male factor	2	2,85%
Two Indications	12	17,14%
Three Indications	2	2,85%
TOTAL	70	100%

Table 2: Distribution of PGD cases, according to the ongoing pregnancy, Goiânia, Goiás, 2014-2019.

Pregnancy	Absolute number (n)	Relative number (%)
YES	17	34,69%
NO	32	65,30%
TOTAL	49	100%

Table 3: Distribution of PGD cases, comparing age range and quality of embryos, Goiânia, Goiás, 2014-2019.

Group	Age	Number of patients	Total number of embryos	Regular embryos	Altered embryos	Amplification failure	Altered embryos %
A	< 35 years*	28	152	61	77	14	50,65%
B	36-39 years*	23	98	28	51	19	52,04%
C	>40 years*	19	77	16	54	7	70,12%
	TOTAL	70	327	105	182	40	-

P value*; Group A x Group B p=0.101; Group A x Group C p=0.002; Group B x Group C p=0.007

Table 4: Distribution of PGD cases, according to the number of embryos per patient and age group, Goiânia, Goiás, 2014-2019.

Group	Age	Number of absolute embryos	Number of patients	Median (95% ci) of embryo per patient
A	<35 years *	152	28	5,00 (4,3-6,6)
B	36-39 years *	98	19	5,00 (3,8-6,5)
C	>40 years*	77	23	2,0 (2,1-4,6)
	TOTAL	327	70	4,50 (3,9-5,4)

P value*; Group A x Group B p=0.751; Group A x Group C p=0.009; Group B x Group C p=0.008

The main changes found were aneuploidies 82.41%, followed by structural changes 13.18%, linked to gene diseases represented 4.39%. Regarding aneuploidies and the number of altered chromosomes, embryos with 1 single altered chromosome represented 40.10%, with 2 altered chromosomes they were 13.18%, and those with alterations in 3 chromosomes were 9.34%. Embryos with 4 or more altered chromosomes were classified as complex, representing 19.78%. Trisomy 16 was the most frequent alteration. Chromosome 22 showed the most changes. (Table 5).

Table 5: Distribution of PGD cases according to the frequency of most frequent chromosomal changes, in Goiânia-GO, 2014-2019.

Main changes	Amount	%
trisomy 16	7	3.84%
trisomy 15	5	2.74%
monosomy X	5	2.74%
monosomy 22	5	2.74%
trisomy 22	4	2.19%
monosomy 5	4	2.19%
trisomy 19	4	2.19%
trisomy 20	4	2.19%
trisomy 13	3	1.64%
monosomy 17	3	1.64%
monosomy 21	3	1.64%
trisomy XYY	3	1.64%
trisomy 21	2	1.09%
trisomy 1	2	1.09%
monosomy 13	2	1.09%
OTHERS*	126	69.23%

*The others had a frequency less than 1%

DISCUSSION

101 assisted reproduction cycles were analyzed, with 70 patients, resulting in 327 embryos, of these, 105 normal and 182 altered, and 40 had amplification failure. The mean age of the patients was 36.86 years, varying between 27 and 44 years. The average age of the partners was 39.2 years, ranging from 26 to 52 years, 3 patients had sperm donation. Among these 105, 49 transfers were made with 52 transferred embryos. The pregnancy rate was 46.95%, with 12.24% abortion, resulting in 34.69% ongoing pregnancies. In the studies presented by Chow et al., in the evaluation of 133 cycles of assisted reproduction, with 65 transfers, patients who underwent PGS and PGD had implantation rates of 45.7%, 41.1% and abortion rates between 8.3 % and 28.6%, respectively [5]. For the frozen embryo group, the rate ongoing pregnancy was 36.4% for the PGS group and 60.0% in the PGD group. For the European Society for Human Reproduction and Embryology, the rates found were 24% for ongoing pregnancy and for implantation, it was 31% per embryo transferred[6]. In a systematic review by Laws, the pregnancy rate ranged from 26.7%-87% [7]. Demonstrated an implantation rate of 64.29% in patients under the age of 35 years. In our study, the implantation rate was 67.69%, in patients in this age group [8]. The main indication was maternal age with 40%, 17.14% of patients had two indications; the third most frequent indication was for the screening of aneuploidies 12.85%.

Comparing the age of the patients with the percentage of embryos altered by the total embryos of each age group, the patients aged less than or equal to 35 years (group A), presented 50.65% of the embryos altered, those aged between 36 to 39 years (group B) had 52.04% embryos altered. Patients aged over 40 years (group C) presented 70.12% of embryonic changes. Lukaszuk et al., had 56.6% of embryos altered, and the percentage of normal, in patients over 40 years old, was 38.5%, with no significant difference with the other age groups [9]. In the current study, group C (> 40 years) presented 20.77% of normal embryos, group B presented 28.57%, and group A 40.13%. When we compared the number of normal embryos in groups A with group B, it showed statistical significance ($p = 0.019$), group A with group C ($p = 0.001$). There was no statistically significant difference between the rates of groups B and C ($p = 0.071$). The total number of embryos was 327 in 70 patients, with a median of 4.67. Regarding the median of embryos by age group, group A presented 5.00 (4.3-6.6), group B presented 5.00 (3.8-6.5) and group C presented 2, 0 (2.1-4.6). The total median was 4.50 (3.9-5.4). When gene-diseases were suspected, the rate of altered embryos was 76.92%. The presence of two indications presented 68% of the embryos altered. The indication of maternal age resulted in 63.96% of altered embryos. Repetition abortion presented 35.84%; the male factor was the indication that resulted in a lower rate of altered embryos 27.27%.

Among aneuploidies, complex changes resulted in 19.70%. Patients with 1 altered chromosome, trisomy 16 was the most prevalent with 7 altered embryos, followed by trisomy 15, Turner syndrome, and monosomy 22 with 5 altered embryos, were the most frequent alterations presented. The trisomy of chromosomes 19,20 and 22 showed 4 altered embryos. Trisomy 13, monosomy 17, and monosomy 22 and XXY had 3 altered embryos. Embryos affected on more than 1 chromosome did not show a repetition pattern [9]. Observed that chromosome 22 had the most changes, representing 15.4% [10] showed a rate of complex changes using 14.7% aCGH. The complex changes in our study accounted for 19.7%. The triploidy rates vary 2%-3% in the literature [11] presented a rate of 0.4%, in the 327 embryos analyzed, no triploidy was diagnosed. Uma revisão recente da Cochrane da ATA demonstrou que o PGS nao deve ser oferecido como atendimento de rotina ao paciente, sob qualquer forma [12].

CONCLUSION

The most common indications were maternal age, screening for aneuploidies and implantation failure. The rate of abnormal embryos increases significantly in the group of patients aged 40 years and over. The main changes found were aneuploidies 82.41%, followed by structural changes 13.18%, linked to gene diseases, representing 4.39%. Among the aneuploidies, there was a higher prevalence of trisomy 16, followed by trisomy 15, monosomy X, and monosomy 22.

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