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Effect of surgical hysteroscopy and PGT-A on pregnancy rates in in vitro fertilization with own eggs

Abstract

Background: *In vitro* Fertilization (IVF) is a tool for assisted reproduction used with the aim of increasing pregnancy rates in couples with infertility issues. These procedures may be optimized using techniques for genetical evaluation of the embryo by means of preimplantation genetic testing for aneuploidy (PGT-A) or diagnosis and correction of the uterine cavity such as Hysteroscopy.

Objective: The objective of this study was to evaluate the impact of hysteroscopy in contrast with PGT-A analysis with respect to pregnancy rates on IVF cycles.

Materials and methods: A study was carried out with Mexican patients during 2018-2021. Patients were divided in two groups: Group 1, patients with guarded prognosis for fertilization; Group 2, patients with guarded prognosis for implantation. The couples evaluated were subjected to different methodologies before IVF.

Results: It was found that prior use of PGT-A or Hysteroscopy increase pregnancy rates by 9.4% up to 20.92%. In Group 1 the use of PGT-A/IVF caused a mean pregnancy rate of 77.7%, being favorable the transference of a single embryo. In Group 2, the best combination was Hysteroscopy/IVF with a pregnancy rate of 76.96%.

Conclusion: Both of the methodologies prior to the IVF cycle improve pregnancy rates, being recommendable to carry out a PGT-A in patients with a poor genetic prognosis with the transference of a single embryo. Hysteroscopy is recommended when lesions or infectious processes are detected in the uterine cavity, and two-embryo transference is carried out.

Keywords: In vitro fertilization, hysteroscopy, pregnancy, aneuploidy screening

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Introduction

Infertility is a worldwide problem that affects up to 12% of couples.[1] In Mexico has been reported that up to 17% of couples have this problem.[2] In Vitro Fertilization (IVF) is a tool for assisted reproduction, effective and applied worldwide based on the in vitro culture of embryos for 3-5 days until developed into blastocyst state in order to be transferred to the uterus with the aim of increasing pregnancy rates in couples with infertility problems.[3]

As any biological process, the IVF technique has multiple factors that determine its success. There are two crucial points in the *in vitro* fertilization process: embryonic development, and the transference. In the first one, embryos may show genetic, morphological, or physiological alterations. To evaluate genetic alterations different methodologies have been developed such as genetic tests subdivided in: PGT-M for monogenic condition, PGT-SR evaluation of structural rearrangements, and PGT-A aneuploidy screening.[4,5] Morphological or physiological evaluation of embryos is carried out in a laboratory, where embryonic quality is categorized according to the compliance of a series of requirements that include: the degree of fragmentation, size, disposition and symmetry of their blastomeres.[6] This helps to avoid the risk of transferring embryos with low survival rates. On the other hand, genetic evaluations seek to avoid the transference of chromosomally abnormal embryos; thus avoiding defects in the fetus.[7] PGT-A is an alternative among the methodologies of genetic analysis, that increase pregnancy rates with the advantage of being quick and safe.[8–10]

With respect to transference, maternal factors have been described that influence the success of the cycle of *in vitro* fertilization, reason for which failures in endometrial receptivity have been observed in patients with abnormalities of the uterine cavity, alteration in endometrial line, alteration of endocrine levels, and alterations in auto-immune responses, triggering an implantation failure. Spath et al.[10] and Shaley et al.,[11] mention that 25% of patients with implantation failure show conditions such as endometriosis, hydrosalpinx, uterine pelvic disease. The evaluation of uterine cavity is a key point in the Assisted Reproduction Technology (ART). Transvaginal ultrasonography, hysterosalpingography, sonography, and hysteroscopy may be used as tools for evaluating the uterine cavity,[12] being the surgical hysteroscopy both, a diagnosis tool and a corrective procedure, which makes it superior to other methods.

The objective of this study was to evaluate the impact of Hysteroscopy in contrast with PGT-A analysis, with respect to pregnancy rates on IVF cycles.

Materials and methods

Selection of the population

In this retrospective, cross-sectional and observational study, a population of 88 Mexican women between 28 and 43 years old was analyzed. Their medical data were collected from data bases of the Research Departments of Clínica Horizontes, and Clínica Pronatal, within the period of 2018-2021. All patients were subjected to a diagnosis to detect endocrine, inflammatory, infectious, and anatomical

factors causing their infertility. As a complement, a transvaginal echography was carried out to evaluate the pelvic anatomy and ovary structure. For academic purposes, they were divided in two groups: Group 1, patients with guarded prognosis for fertilization (failure of embryonic development) including couples with alterations of male factors, and ovarian endocrine disruption. Group 2 included patients with guarded prognosis for implantation (transference failure) and those couples with alteration of anatomical uterine factor and/or infection were taken into account.

The couples evaluated were subjected to different methodologies complementary to *in vitro* fertilization: hysteroscopy, PGT-A, or none. Controls were constituted by patients that went through IVF cycle with no previous methodologies (no PGT-A or hysteroscopy were performed) (n=23). The patients subjected to a genetic PGT-A complementary to IVF, were designated as *PGT-A* (n=39), and those who opted for surgical corrective methodology complementary to IVF, were designated as *Hysteroscopy* (n=26).

Embryonic biopsy for preimplantation genetic testing

The degree of expansion, the characteristics of the inner cell mass (ICM), and trophectoderm cells, were evaluated to determine the day of biopsy. A Biopsy needle MBBBP-30 Origio Inc. (Chartottesville, VA, USA) was used, and to hold the embryos a Holding needle MPH-SM-30 Origio Inc. (Chartottesville, VA, USA) was used. Four to six trophectoderm cells were taken with the micromanipulator by detaching them from the blastocyst with the help of a laser (Zilos Tk, Hamilton Thorne Biosciences) directed to the surface of the collapsed zone with a pulse intensity of 400 microseconds each at 100% of power. Then, the cells studied were kept frozen at -78ºC (dry ice) to send them to the laboratory where the preimplantation genetic testing was performed.

Preimplantation genetic testing

DNA of each sample (biopsy of trophectoderm cells) was extracted and amplified by the procedure of Whole Genome Amplification (WGA), and a molecular study was performed using Next Generation Sequencing (NGS) Technology, ILLUMINA® - VeriSeq PGS. This analysis allows detecting numeric anomalies of the 46 chromosomes including the sexual ones. The analysis was performed using two references (male and female) as internal controls.

Hysteroscopy

In some cases a surgical hysteroscopy procedure was performed along with egg retrieval, and in other cases, during endometrial preparation. Before anesthesia, the patient was placed in lithotomy position, proceeding to the cleaning and surgical preparation. Hysteroscopy was carried out using a rigid 8 mm Betocchi hysteroscope with anterior port, and insufflation of the uterine cavity with 9% physiological solution. When the cervical os was at sight, the procedure was started by introducing the hysteroscope through the cervical canal to the uterine inlet. Both of the ostia were located and an exploration of the fundus of the uterine cavity was performed. In all cases, corrections with bipolar electrocautery of flamed and cottony lesions were performed, and then, a 5 mm wide transverse lesion was made in the uterine fundus with the intention of re-epithelializing the endometrial tissue. In cases with visualization of septa, polyps, adhesions or myomas, these were extracted by means of radiant energy. Hemostasis was corroborated and energy was applied to the Naboth cysts found within the cervical canal. In all cases a post-intervention protocol of analgesic and anti-oxidant treatment was performed, and hormone replacement protocol for hormonal and endometrial preparation was started for embryo transfer.

Embryo transfer

In all cases, the embryo transfer was made with own eggs. All patients had an endometrial preparation with cycle monitoring by ultrasound and estradiol biochemistry. Embryo transfer was performed with endometrial thickness of 6-12mm and estradiol higher than 250pg/dL with tendency to increase. The protocol was started with a standard dose of progesterone according to international reports.[6] The transfer was guided by ultrasonography with a Wallace cannula, with an average shot at 1.5 to 2cm from the uterine fundus. Pregnancy confirmation was performed 12 days after embryo transfer.

Statistical analysis

For this study, data on age and number of embryos are reported as the mean ($\bar{X}$) ± SD. Pregnancy rate results are expressed as percent with a 95% confidence interval by Pearson's Chi-square (χ^2) statistical analysis. In all cases, a P value <0.05 was considered as a statistically significant difference. Statistical analysis was carried out with the statistics software InfoStAt version 2020-I (Grupo Infostat, FCA, 2002).

Results

This study included 88 patients with an average age of 36.29±0.347 years old, which were divided in two groups according to their infertility diagnosis: Group 1, (poor prognosis for embryonic development), and Group 2, (poor prognosis for implantation), and also according to the effect on IVF cycles. A comparison was made between the methodologies evaluated (PGT-A, and Hysteroscopy). Group 1 included a total of 40 patients, while in Group 2 48 patients were analyzed.

Pregnancy rates in the population were quantified according to the methodology evaluated. It was found that the patients in Control Group had an average rate of 52.1%. In contrast, those patients that opted for the PGT-A methodology as a complement to their treatment showed an average rate of 61.5%, and those that opted for hysteroscopy as a complement to their treatment showed an average rate of 73.02%, which represents a statistically significant difference with respect to the Control Group (Figure 1).

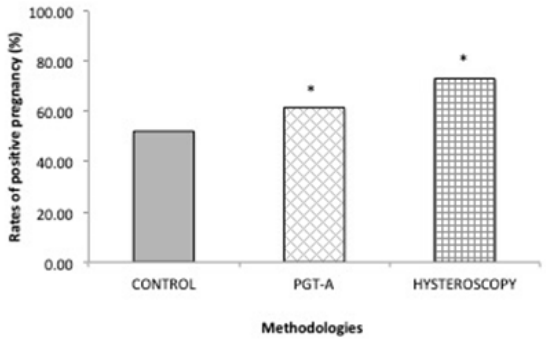

Figure 1 Rates of positive pregnancy (n = 21-39). Values significantly different to the Control are represented with "*" according to the χ^2 statistical analysis (P<0.05).

In Group 1, the Control showed a pregnancy rate of 53.84%, while those patients that opted for the use of complementary methodologies such as PGT-A, and Hysteroscopy, showed a statistically significant increase in pregnancy rates, with values of 77.7%, and 88.7%, respectively (Table 1). In Group 2, the patients of the Control Group showed a pregnancy rate of 47.62% in contrast to those subjected to PGT-A, who showed an increase of 2.38%; on the other hand, patients

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that opted for Hysteroscopy showed an increase of 17.08% with respect to the Control (Table 1).

Table 1 Effect of methodologies complementary to the treatment by IVF. Pregnancy rates in Mexican women (n = 9-21). The values significantly different to Controls are represented with "*" according to the χ^2 statistical analysis (P<0.05)

	Pregnancy rates in Mexican women (%)	
IVF	**Group I**	**Group II**
Control	53.84	47.62
PGT-A	77.77*	50
Hysteroscopy	88.8*	64.70*

With respect to the number of embryos transferred, the pregnancy rate in each Group was as follows: The case of a single embryo transfer, and its relationship with each Group is described below. For Group 1, patients of Control Group showed an average pregnancy rate of 53.84%, in contrast to those of the Group PGT-A/IVF, which showed a pregnancy rate of 81.25%, that represents a statistically significant difference with respect to Control (Figure 2a). In Group 2, pregnancy rates of 43.75%, and 25%, were found for PGT-A/IVF and Hysteroscopy methodologies, respectively (Figure 2a).

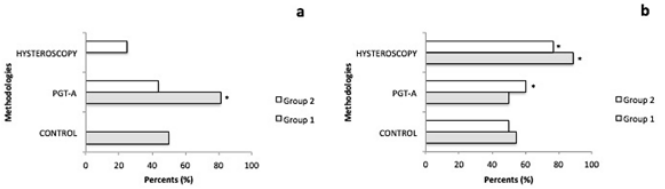

Figure 2 Effect of methodologies on pregnancy rates. a) Evaluation with single embryo transfer (n = 2-14), and b) two embryos (n = 28). Values significantly different to the Control are represented by "*" according to the χ^2 statistical analysis (P<0.05).

When the embryo transfer was performed with two embryos, it was found that the pregnancy rate of patients of Group 1 was 54.5% compared to the group of PGT-A and Hysteroscopy, where the values obtained were 50%, and 88.8%, respectively (Fig. 2b). The differences with respect to the Control were statistically significant. In Group 2, the pregnancy rate of Control group was 50% (Figure 2b). Those patients subjected to PGT-A/IVF methodologies showed an increase of pregnancy rate of 10% with respect to the Control, with a significant difference. On the other hand, patients of the Hysteroscopy / IVF group showed an average pregnancy rate of 76.92% (Figure 2b).

Discussion

In this study it was found that prior use of methodologies such as genetic diagnosis (PGT-A) and implantation in uterus (Hysteroscopy), may increase the pregnancy rates in 9.4-20.9% in Mexican women with infertility problems (Figure 1). The age of women is a relevant factor in pregnancy rates; in this study, a group of women with an average age of 36.9±0.347 years old was evaluated, age that is similar to that reported for the evaluation of pregnancy rates by IVF.[12,13]

The evaluation of embryo quality during IVF cycles avoids the transference of embryos with genetic abnormalities or low implantation rates. Pechapanich Y, et al.,[14] reported that the use of PGT-A followed by IVF in patients older than 35 years old, showed an increase up to 40%, which is similar to that found in this study, where the patients that opted for the use of PGT-A / IVF showed pregnancy rates of 77% and 50% for Group 1 and Group 2, respectively (Table 1). The differences between the groups may be due to the fact that in Group 1 patients with guarded prognosis for a suitable embryonic development were recruited. Genetic diagnosis by PGT-A has shown to increase pregnancy rates by reducing the transference of embryos with chromosomal abnormalities,[14,15] as there are reports where high rates of aneuploidies may be related to causes of infertility [16,13]; thus, the use of genetic diagnosis tools assures the embryo quality in patients with poor prognosis related to embryonic development.

An evaluation of the number of embryos transferred and their effect on pregnancy rates was also carried out, which demonstrated that a genetically healthy single embryo reach pregnancy rates of 81.25% (Figure 2a), compared to the control group that showed a pregnancy rate of 43.75%. In contrast, by transferring two embryos in Group 1, pregnancy rates of 50% were found, and the increase was significant only in Group 2 in this combination (PGT-A/IVF). Contrary to the findings of this study, there are reports where the transference of one or multiple embryos does not show any effect on pregnancy rates.[16,17]

Similarly to the evaluation of embryo quality, another critical point to achieve pregnancy is the embryo transfer, where the patient's physiological conditions have a critical role. Simon et al.[18] have reported that implantation failures have been poorly explored. They are a multifactorial issue for which a timely diagnosis of structural uterine problems and their correction increase the success of the IVF process.[18,19]

Surgical Hysteroscopy is a tool that provides the opportunity to observe the uterine cavity and the existence of anomalies that may be corrected by surgery. It has advantages such as the assessment of the functionality of the cervical canal, helping with the study of abnormal uterine hemorrhages, and to confirm the anatomical and functional integrity after repetitive failures of IVF; making it possible to rule out uterus-endometrial alterations with a partial resolution, and to treat endouterine pathologies.[20] There are reports that have found increases in pregnancy rates when a surgical hysteroscopy has been performed before IVF treatment.[20,21] Few studies have been carried out in Mexico about the combined use of hysteroscopy prior to IVF.[22]

In this study, the performance of hysteroscopy/IVF showed to increase pregnancy rates by 20.97% with respect to the Control (Figure 1). Similarly, there are reports of a 13% increase in pregnancy rates in women subjected to hysteroscopy/IVF after two or more unsuccessful cycles.[23,24] Some authors suggest to perform hysteroscopy in a third cycle;[24] however, other authors contrast with this idea and suggest that it has to be performed since the first IVF cycle when there is any previous clinical history.[21,25] With this study it may be evidenced that couples with infectious processes or uterine abnormalities may benefit if hysteroscopy is performed prior to IVF cycle.

When the classification between designated groups was made, it was found that in Group 1 pregnancy rates increased by 34.96% (Table 1), while in Group 2 pregnancy rates increased by 17.1% (Table 1), which indicates that this methodology provides a general improvement of pregnancy rates. Accordingly, it is proposed to consider genetic studies with endocrine ovarian and male factor alterations, and to consider hysteroscopy to contribute to the improvement of pregnancy rates in patients with endometritis, EPIC, and anatomical alterations of quality, and not only in patients with implantation failure in the IVF cycle.[26,27]

Considering the effect of the number of embryos transferred after hysteroscopy, in Group 1 no patients complying the classification criteria were found; however, when two embryos were transferred, pregnancy rates were estimated in 88.8%. The above indicates that there may be changes in the body caused by hysteroscopy that modify implantation rates.

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With respect to the results of Group 2, the transference of a single embryo showed a result of 25% (Figure 2a) compared with a rate of 76.96% when two embryos were transferred (Figure 2b). Smith et al.,[28] speculate that hysteroscopy may lightly improve the conditions for the implantation of less vital embryos, resulting in an increase of pregnancy rates but with the risk of being biochemical pregnancies or loss.

Conclusion

PGT-A is a tool useful for genetical embryonic evaluation in patients with infertility and recurrent pregnancy loss. Therefore, it is recommended to be performed in patients with poor genetic prognosis, being favorable the transfer of a single embryo.

It is also recommended to perform hysteroscopy in patients subjected to IVF when uterine lesions or infectious processes are detected in the endometrial cavity, as there is statistically significant evidence that this procedure increase pregnancy rates in patients to whom two embryos were transferred.

In contrast, the use of one or the other methodology provides an increase of pregnancy rates in patients with infertility, compared to those patients that opt for direct IVF cycle(s).

Scope and limitations

This study proposes the use of methodologies (PGT-A and Hysteroscopy) complementary to the performance of IVF cycle(s) in Mexican women.

In this study, the contrast between the number of embryos and their effect on pregnancy rates was performed, being inconclusive with respect to the transference of one embryo due to the lack of patients that comply with the classification parameters for their evaluation in all groups.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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