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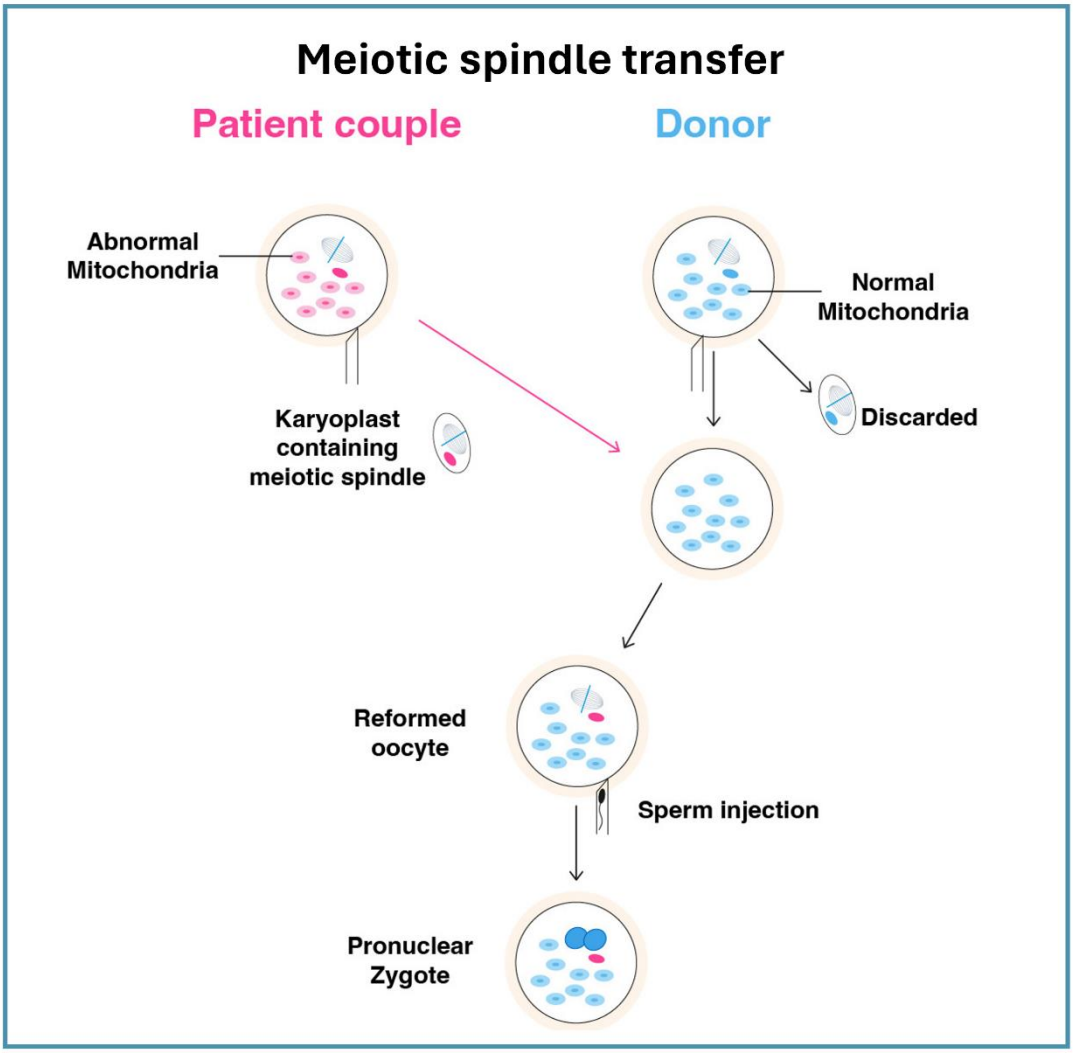

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The Journal of Reproduction

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The Journal of Reproduction

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Editorial

Asch-Schuff Ricardo Héctor[1], 0000-0001-5743-7121.

Dear Readers,

As we approach the culmination of another remarkable year, we at The Journal of Reproduction take immense pride in reflecting on the accomplishments and strides achieved in the realm of reproductive medicine. The collective efforts of our dedicated team have resulted in an issue brimming with high-quality content that promises to captivate clinicians, researchers, and bioethicists alike.

Diversity has been a hallmark of this year's publications, with manuscripts hailing from various corners of the globe and addressing subjects seldom explored in other reproduction journals. The thought-provoking articles on alternatives to oocyte donation, in particular, promise to ignite significant discussions within the scientific community. These unique contributions serve as a testament to the innovative spirit that drives the field of reproductive medicine forward.

Gestational surrogacy, often overlooked in other reproduction journals, takes center stage in this issue. The manuscripts presented showcase some of the finest experiences and real-world results, reaffirming our commitment to inclusivity and a comprehensive exploration of reproductive practices.

Beyond these groundbreaking topics, our collection of reviews and opinions from global experts challenges us to think differently about our respective fields of practice and research. Each piece invites readers to consider new perspectives, fostering a dynamic intellectual environment within our community.

As we draw the curtain on this year, we find ourselves eagerly anticipating the promise of 2024. The forthcoming articles, already in the pipeline, hold immense scientific and clinical significance, setting the stage for another year of groundbreaking discoveries and advancements in reproductive medicine.

Our heartfelt gratitude extends to our esteemed Editorial Board, Editorial Committee, Publisher, and, most importantly, to you—the readers. Your unwavering support has been instrumental in making The Journal of Reproduction a platform for cutting-edge research and insightful discourse. As the holiday season approaches, we extend our warmest wishes to each of you. May it be filled with joy, good health, and moments of reflection.

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Here's to a splendid end to 2023 and the promise of a fantastic 2024—a year that we are confident will bring even greater contributions to the fields of science and medicine.

Warm regards,

Asch-Schuff Ricardo Héctor
Editor in Chief

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Does Mitochondrial Transfer An Alternative to Egg Donation?

Birol Aydin

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ABSTRACT

Objective

To evaluate the utility of pronuclear transfer using healthy oocytes from donors in poor prognosis patients.

Design

Retrospective study.

Subjects

A total of 29 patients with no blastocyst development or total fertilization failure were included.

Main Outcome Measures

Our primary outcome was the blastocyst rate. Secondary outcomes measures included euplody rate, clinical pregnacy rate and live birth rate.

Results

On day 5/6 of blastocyst development, an average blastocyst rate of 49.2% was obtained. The average rate of euploid blastocysts obtained after PGT-A was 69.5%. All patients underwent frozen embryo transfer. Single blastocyst transfer was performed in all patients, and the clinical pregnancy rate was 48.3%. Of these patients, 14 had a live birth, and the live birth rate was 48.3%. No genetic or morphologic abnormalities have been detected in the babies born. The 29 patients were grouped based on their age, as <35 (n=2), 35-27 (n=6), 38-40 (n=9), 41-42 (n=6) and >42 (n=6). Based on these age groups, blastocyst formation rates were 47.8%, 50.0%, 45.0%, 50.0% and 66.7%, respectively; euploidy rates were 63.6%, 61.1%, 66.7%, 100.0% and 83.3%, respectively; clinical pregnancy and live birth rates were 100.0%, 50.0%, 44.4%, 50.0% and 33.3%, respectively.

Conclusions

The results of this study show that pronuclear transfer can result in a high blastocyst formation rate, euploidy rate and live birth rate. This was shown among patients across all age groups, particularly in older patients who often show diminished IVF success rates.

KEYWORDS: Mitochondria, egg donation, reproductive age, embryo development, mitochondrial transfer.

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MANUSCRIPT

Introduction

Mitochondria are found in eukaryotic cells, with their most important function being their role in producing adenosine triphosphate (ATP). Mitochondria are present in most cells of the body, generally in numbers between 100-1000[1] and carrying 2-10 copies of mitochondrial DNA (mtDNA)[2]. While the function and activity of mitochondria vary based on cell type, mitochondria generally play a role in oxidative phosphorylation, metabolic balance, cellular senescence, and maintenance of apoptotic mechanisms[3]. Damage to mtDNA can result in mutations that can lead to many mitochondrial disorders. In particular, heteroplasmy in the tissues and organs of the fetus during fetal development can lead to the formation of mtDNAs with different mutant ratios and hence a qualitative transmission to the next generation.

In some cases, although the mitochondria in a mature oocyte (metaphase II) show a morphologically homogeneous structure, they may exhibit different effects depending on the level of mitochondrial polarity. Mitochondrial polarity refers to the electrical charge on the inner membrane, which is directly related to ATP energy production. A mitochondrion with a high membrane potential has a high rate of ATP production and plays an essential role in regulating CA^{++} hemostasis[4]. Mitochondria undergo changes during fertilization, embryo development, and preimplantation. During metaphase I and II in the oocyte, mitochondria are homogeneously distributed throughout the cytoplasm, and an abnormal distribution of this homogeneous distribution through a network of microtubules could be detrimental to the fertilization of the oocyte and the developmental properties of the embryo. Therefore, structural changes in mitochondria affect the quality, potential, and development of the oocyte.

The correct mitochondrial functioning required for suitable oocyte development and embryonic development after the fertilization. Most probably intra cellular energy transferring may interrupt and it directly affect mitochondrial disfunction. Mitochondrial disfunction will bring limitation for ATP energy transport and it may give interruption to morph kinetic development of embryo right after cleavage stage. Mitochondrial dysfunction can be led by lack of energy or morphological abnormalities on the mitochondria. Both ways may create limitation for embryonic development and oocyte ageing in advance maternal age.

Mitochondrial Diseases and Mutations

PGD has been used in different ways, particularly to determine the number of mitochondria that may carry the mutation as the fetus grows. This technique aims to transfer embryos with a low risk of mutant mtDNA on a 6-10 cell basis in trophectoderm biopsy samples obtained from embryos obtained using the IVF technique. However, PGD technology is limited in its ability to provide results only for mitochondrial mutations and diseases caused by nuclear DNA. Mutations in mitochondrial DNA increase the risk of affecting embryos due to maternal involvement of mitochondria. Due to the lack of techniques particularly for estimating the degree of heteroplasmy in mtDNA, it is not easy to predict the risks associated with mtDNA[5]. In this regard, mitochondrial transfer techniques have been successful in ensuring a healthy subsequent live birth in generations where mtDNA mutations have been detected.

Aging Oocyte

Mitochondria have a crucial role in the process of aging and metabolic decline, especially as a major source of reactive oxygen species. Increased levels of reactive oxygen species result in less mitochondrial energy being metabolically available **(Figure 1)**. As age progresses, molecular senescence progresses to an advanced stage as increased levels of ROS affect mtDNA genome proliferation and both the morphological capacity and metabolic capacity of the oocyte are reduced[6]. The increased level of aneuploidy, in particular, can be explained by the fact that, as meiosis is reactivated, a greater amount of intracellular mitochondrial energy will be needed, and this ATP energy is lower in older patients.

Advanced Maternal Age and Mitochondria

Recent changes in living conditions, changes in women's social status, and postponement of childbearing due to career and occupational priorities have created the problem of achieving pregnancy at advanced reproductive age. The recognition that mitochondria are the center of quality power, especially in the oocyte cell, has confirmed that mitochondria play an important role in the problem of embryonic development at advanced age. In the normal process, paternal mitochondria are captured by autophagosomes and transferred to lysosomes for degradation after fertilization. Here, due to aging, mitochondria begin to show morphological changes and impaired activity. The loss of mitochondrial energetic activity at an older age has been associated with problems in the transition of embryos from cleavage to blastocyst at the cleavage stage of embryo development when energy requirements are high. The use of young mitochondria in these patients has been

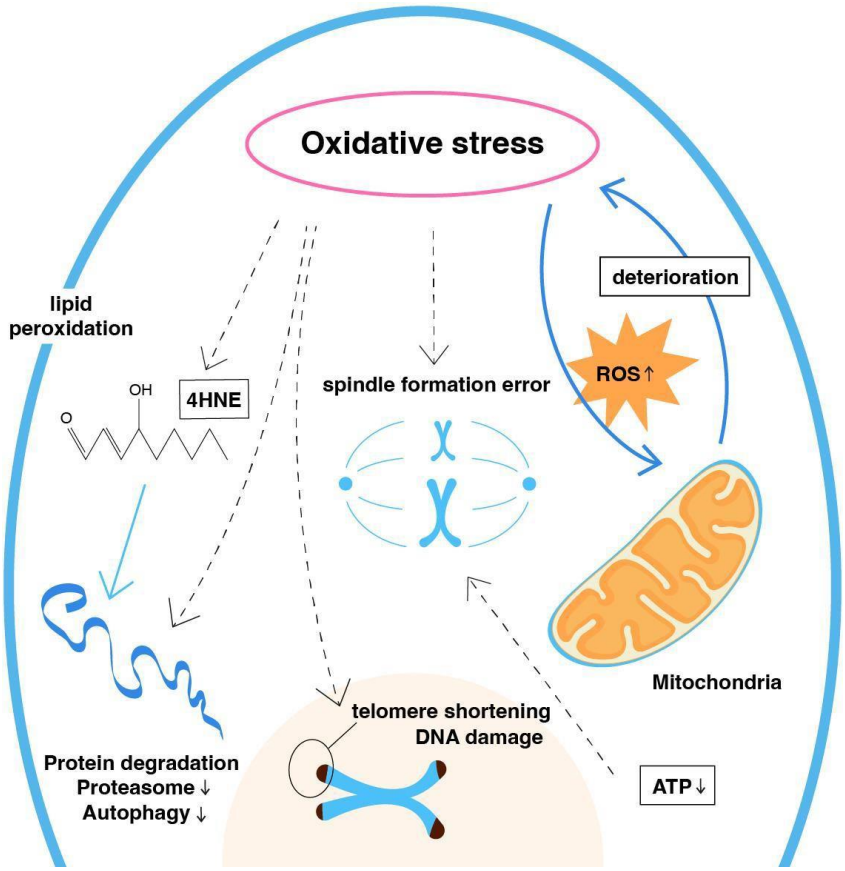

Figure 1. Mitochondria aging by oxidative stress.

shown to significantly increase the rate of blastocysts obtained from embryos. In oocyte donation, it is observed that embryos obtained from oocytes obtained from young donors can easily achieve pregnancy when transferred to elderly patients. The most significant finding here is the high rate of euploid embryos in young patients, which leads to a higher chance of pregnancy success. Additionally, it has been observed that young oocytes had a high euploid rate, and euploid embryos were obtained from euploid oocytes. In both mouse and other animal experiments, it has been found that older oocytes had both a very low euploid rate and very low mitochondrial activity. It has also been noted that older women have much lower mtDNA at the zygote stage than younger women and that embryos from these zygotes do not reach the cleavage stage to the blastocyst stage.

Mitochondrial Regulation in Oocyte Development and Function

Results from different studies have proven that pyruvate, rather than glucose, is necessary for the maturation and maintenance of the oocyte. In this regard, the active use of pyruvate and the maintenance of the oocyte depends on the amount of mitochondrial activity. The maturation and maintenance of the oocyte are ensured by the production of ATP by the mitochondria and the beta-oxidation of fatty acids[7]. The dynamic structure of the mitochondria splits in two with the formation of fusion and shows cellular distribution, including in cumulus cells. During this fragmentation, almost all of the asymmetrical mitochondria remain inside the cell. All this process takes place in Meiosis I, while the mitochondria are completely incorporated into the cytoplasm in Meiosis II. The maximum level of ATP generated during this process, together with the Ca++ pathway through the Endoplasmic Reticulum, utilizes this energy for cellular development and embryo maintenance. The most critical situation here is the transmission of heteroplasmy between generations. Heteroplasmy represents more than one mitochondrial DNA variant present in the cell and each individual carry one. The degree to which a person carries the disease based on heteroplasmy and its intergenerational transmission also indicates the extent of the mitochondrial mutation[8].

Mitochondrial Donation

Using a fertility-proven donor oocyte with healthy mitochondria, especially in diseases related to mitochondrial mutations, eliminates the risks and

ensures the formation of healthy embryos. For various reasons, many patients with mitochondrial disease are diagnosed late, and due to the advanced age at which treatment is started, both the quality and quantity of oocytes are limited. Naturally, blastocyst development is very limited in patients with this advanced age characteristic. With the identification of good embryo development in these elderly patients, it was realized that mitochondrial transfer may be an alternative to oocyte donation in elderly patients. This method utilizes the mitochondrial potential of high-quality donor oocytes to produce high ATP energy, resulting in high-quality blastocysts in many patients. However, progress in correcting chromosomal defects in embryos obtained by this method is limited.

Meiotic Spindle Transfer

The meiotic spindle is the structure that forms during anaphase between meiosis 1 and meiosis 2, and it also serves to transport centrosome proteins. The meiotic spindle has a fundamental role in the development and genetic structure of the oocyte. The formation of the meiotic spindle by the separation of the chromosome package in the first anaphase phase indicates that the transfer of chromosomal structure occurs in the later stages of embryonic development. Therefore, it can be hypothesized that the transfer of the meiotic spindle from the oocytes of older women to the young donor oocyte results in a much better morpho-kinetic development with higher mitochondrial energy and even a lower aneuploidy rate.

Oocytes from an older patient and young donor stimulated with the same trigger timing should be prepared for transfer by determining the location and size of the spindle using spindle imaging software and polarizer, if the oocyte is mature, immediately after separation of the cumulus complex structure. The 24-hour prior addition of Cytochalasin B to the incubated single-step culture medium protects the zona permeability and cytoplasmic structure of the oocyte during micromanipulation. The spindle is removed using spindle view technology with the help of a small transitional zone to be opened using the laser hatching method in the zone of the oocytes taken from both the elderly patient and the oocyte donor, and the spindle is removed and subjected to fusion in the HVJ-E virus **(Figure 2)**. This process aims to eliminate DNA fragments from the cytoplasmic structure around the spindle and to transfer the spindle into the donor oocyte as a compact DNA carrier. Instead of the spindle removed from the donor oocyte, the spindle structure of the older patient is transferred similarly, and the oocyte is incubated in the prepared solution for a while to ensure the formation of a complete karyoplast. After this procedure, the oocytes are incubated for 1 hour, and then fertilization is performed using the piezzo ICSI procedure.

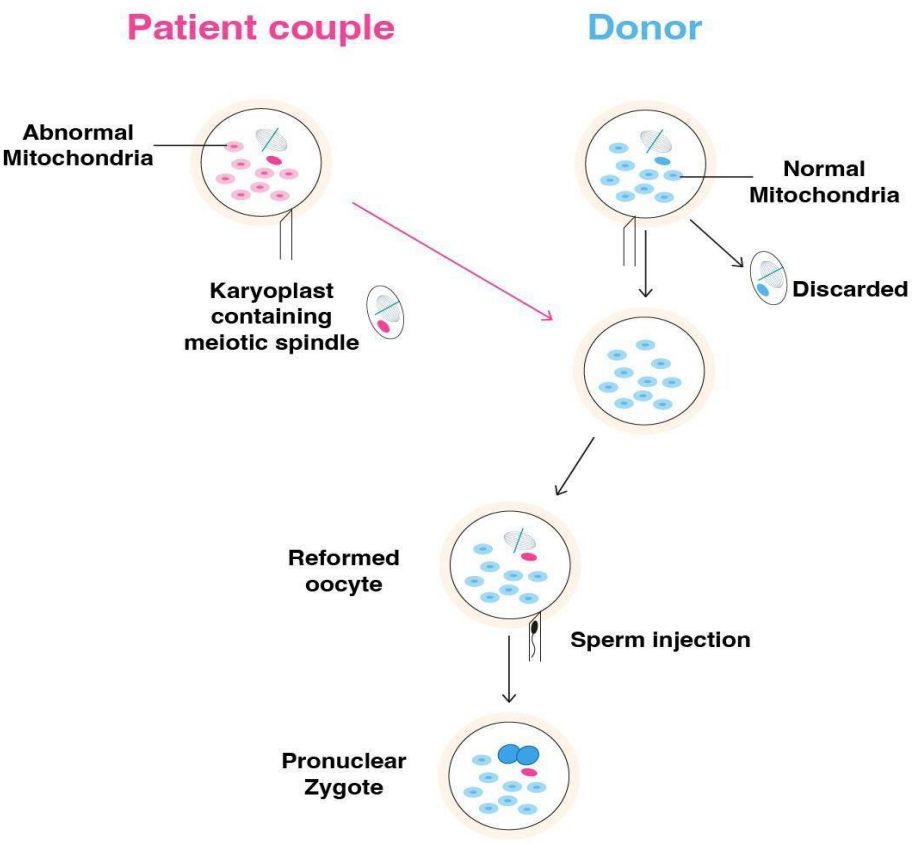

Figure 2. Meiotic spindle transfer.

Pronuclear Transfer

In patients of advanced maternal age, pronuclear transfer can be used as an alternative to spindle transfer, especially in the absence of a history of fertilization issues. The pronuclear transfer would be a good alternative, especially when oocyte quality is poor, and meiotic spindle structure cannot be observed. Another advantage of the pronuclear transfer procedure is the possibility of working on frozen zygote samples. Here, the zygote of an elderly patient can be used frozen, whereas a fresh zygote with fresh donor oocyte collection and a fresh fertilization process needs to be preferred for micromanipulation. Particularly after the ICSI procedure, early pronucleus detection ensures a better quality and successful micromanipulation procedure. Nocodozale and Cytothalasine B are added to the single-step culture medium incubated 24 hours before the procedure to preserve the zona permeability and cytoplasmic structures of donor and elderly patient zygotes in the petri dish. A crossing point is created using laser hatching on the zona of the zygotes, and with the help of a biopsy pipette, nuclei are extracted from both zygotes and introduced into the HVJ-E virus for fusion. The main purpose of this procedure is to transfer the compact DNA structure from the nucleus into the donor zygote by neutralizing the cytoplasmic fragments around the nuclei. After the transfer, the zygotes are left for a certain period to complete the karyoplast process and then transferred into the single-step culture medium, and embryo development is monitored. **(Figure 3).**

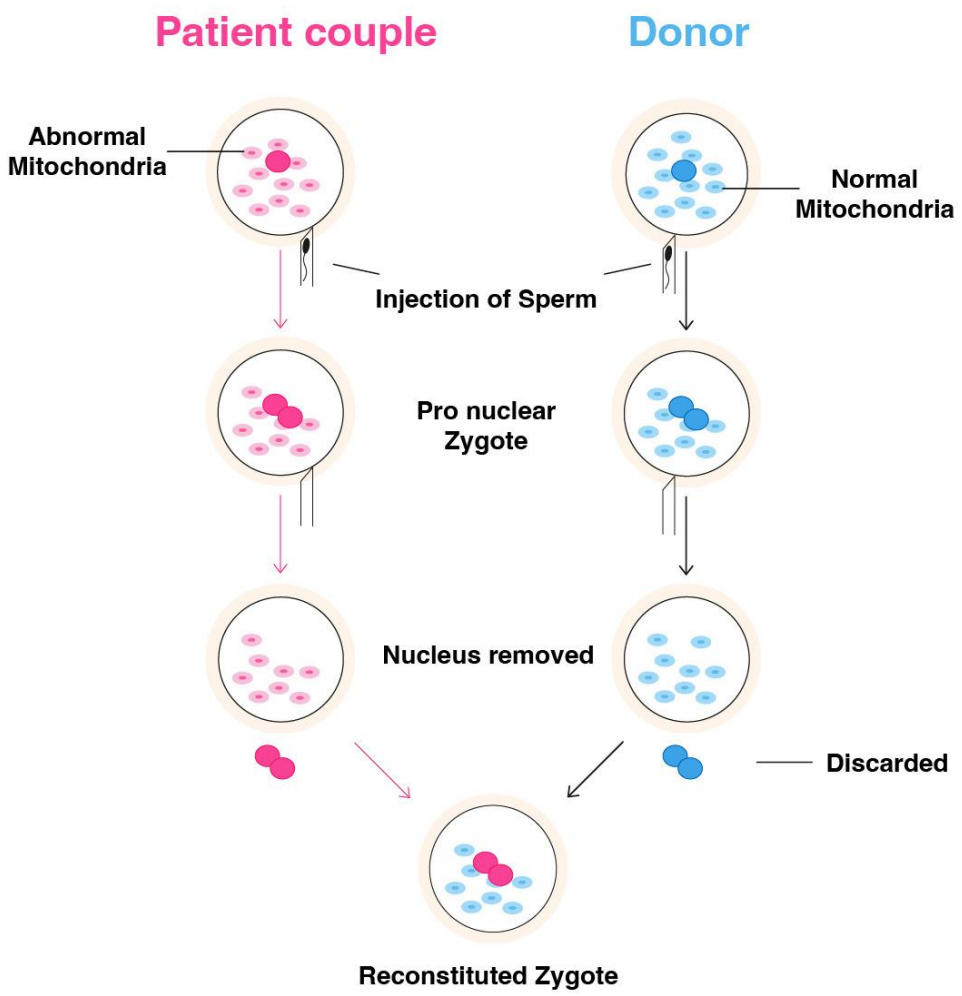

Figure 3. Pronuclear transfer.

Material and Methods

A total of 30 patients with no blastocyst development or total fertilization failure were included in the evaluation. Patients selected whom have minimum 5 IVF trials by ICSI technique with no receiving any blastocyst stage embryo. Patients selected with different AMH levels as between 0.7-2.0. All oocytes collected post trigger 35 hour and all oocytes fertilized after 3 hours from egg collection process and only ICSI technique used for fertilization. Embryo culturing process done by single step culture media and all embryo transfer done after PGT-A testing as frozen embryo transfer. All donor oocytes and zygotes used as fresh and spinal evaluated prior fertilization and mitochondrial transfer. The patients underwent pronuclear and meiotic spindle transfer procedures, embryo development was monitored, and chromosomal evaluation of the embryos was performed using the PGT-A technique. All donors selected for the procedure were fertility proven donors. Donors with at least 1 healthy child and at least 1 live birth in the oocyte donation procedure were determined and included in the procedure. A total of 297 oocytes from all patients were subjected to mitochondrial transfer. There was no loss of oocytes or zygotes after micromanipulation. No degeneration or morphologic damage was detected. The mean age of the patients who underwent the procedure was 39.4 years.

Result

A total of 29 patients elected to perform pronuclear transfer using healthy oocytes from donors, including 137 oocytes. After the procedure, 120 oocytes were fertilized (fertilization rate 87.6%).

When considering all 29 patients, and in terms of embryo development, 113 of the 120 fertilized oocytes progressed to the cleavage stage and 59 progressed to the blastocyst stage on day 5 or 6 (blastocyst formation rate 49.2%). All 59 of these blastocysts were biopsied for PGT-A, with 41 testing as euploid (euploidy rate 69.5%). A single euploid was transferred to each of the 29 patients, leading to 14 clinical pregnancies (clinical pregnancy rate 48.3%) and 14 live births (live birth rate 48.3%), without any pregnancy losses **(Figure 4)**.

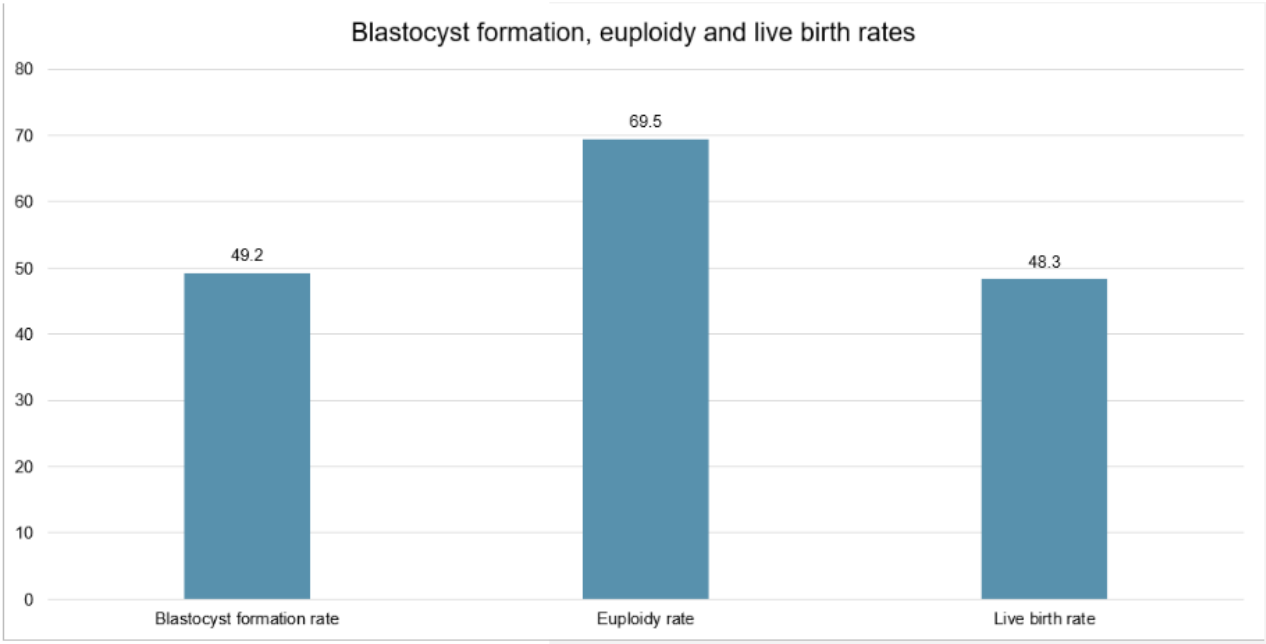

Figure 4. Blastocyst formation, euploidy and live birth rates.

The 29 patients were grouped based on their age, as <35 (n=2), 35-27 (n=6), 38-40 (n=9), 41-42 (n=6) and >42 (n=6). Based on these age groups, blastocyst formation rates were 47.8%, 50.0%, 45.0%, 50.0% and 66.7%, respectively; euploidy rates were 63.6%, 61.1%, 66.7%, 100.0% and 83.3%, respectively; clinical pregnancy and live birth rates were 100.0%, 50.0%, 44.4%, 50.0% and 33.3%, respectively **(Table 1)**.

Although we recommend genetic testing for mitochondrial mutations for all babies born after pronuclear transfer, only 3 of the patients shared their results, which showed no abnormalities.

	Blastocyst formation rate	Euploidy rate	Live birth rate
<35 (n=2)	47.80%	63.60%	100.00%
35-37 (n=6)	50.00%	61.10%	50.00%
38-40 (n=9)	45.00%	66.70%	44.40%
41-42 (n=6)	50.00%	100.00%	50.00%
>42 (n=6)	66.70%	83.30%	33.30%

Table 1. Blastocyst formation, euploidy and live birth rates according to age groups.

The fertilization rate after micromanipulation was 92.4%. While 6 of the patients had total fertilization failure previously, the fertilization rate obtained from 59 oocytes obtained from these patients was 89.25%. Regarding the cleavage development of the embryos, the development rate was determined as 85.74% based on the 3rd day of development. Based on 5th-day and 6th-day blastocyst development rates, only blastocysts with AA, BA, and BB quality were evaluated using the Gardner Scoring Method, and all blastocysts were evaluated with the PGD-A technique by performing trophectoderm biopsy procedures. On the 5th and 6th day of blastocyst development, an average blastocyst rate of 60.28% was obtained. The average rate of euploid blastocysts obtained after PGT-A was 60.68%. All patients underwent frozen embryo transfer. Single blastocyst transfer was performed in all patients, and the clinical pregnancy rate was 46.97%. Of these patients, 13 had a live birth, and the live birth rate was 48.28%. No genetic or morphologic abnormalities have been detected in babies born after live birth.

Discussion

This study aimed to report on blastocyst formation and euploidy rates of patients undergoing pronuclear transfer, demonstrating a 49.2% blastocyst formation rate and 69.5% euploidy rate.

All these patients failed to produce blastocysts after a minimum of 6 previous IVF cycles. The large increase in blastocyst formation rates seen in these patients is likely due to the donor mitochondria providing sufficient energy to power multiple cell divisions.

Six of these 29 patients in this study had previous IVF cycles with total fertilization failure, and after pronuclear transfer, the fertilization rate for these patients increased to 79.3% (based on 29 oocytes).

We performed pronuclear transfer on 29 patients of varying age, with most patients aged 38 and over, all of which demonstrated a high proportion of euploid embryos after PGT-A.

According to a recent report on the distribution of PGT-A results by age, the proportion of biopsied embryos that are euploid declines with advancing age, from 57.7% in patients aged <35 to 16.4% in patients over the age of 42. Our study demonstrates that reconstituted zygotes by pronuclear transfer show a high euploidy rate regardless of age. Although the sample size is small, of the 6 blastocysts generated in patients >42, 5 of them were euploid. This gives a euploidy rate of 83.3%, which is much higher than what would be expected at this age.

To the best of our knowledge, this is the first time that it's been shown that blastocysts by pronuclear transfer have high euploidy rates, irrespective of age. This is likely due to the highly functional donor mitochondria providing sufficient energy.

There are several limitations in this study, including the retrospective design and small sample size. We were also unable to collect more information on the 14 children born.

All clinical treatment methods are open to criticism and are based on a full assessment of the risks involved. Mitochondrial transfer should be considered with the main objective of eliminating the risks associated with mitochondrial diseases. Diseases due to mitochondrial mutations are mostly seen in elderly patients. Mitochondrial transfer has shown good results in problematic embryo development in diagnosed patients who want to have a healthy child at an advanced age, suggesting that this technique can be used in elderly patients. The healthier children born through this method can lead to healthier families and a healthier social structure. In the case of older patients, the ethical imperative is to provide an alternative to oocyte donation, based on the fact that each individual has the right to carry his or her own genetic material or DNA structure. The postponement of the desire to become a mother for sociological reasons has led to various reproductive problems in patients of advanced maternal age, and oocyte donation has become the only alternative for these patients due to decreased ovarian reserve and

decreased oocyte quality. This has led to a significant increase in oocyte donation around the world, with the particular risk that the genetic makeup may not be preserved, and future generations may not carry the same genetic makeup as the family. The alternative to that would be mitochondrial transfer, which offers the possibility and hope that patients can pass on their DNA structure to future generations.

Conclusion

The results of this study show that pronuclear transfer can result in a high blastocyst formation rate (49.2%), euploidy rate (69.5%) and live birth rate (48.3%). This was true among patients across all age groups, particularly in older patients who often show diminished IVF success rates.

The main disadvantage of pronuclear transfer is that, ethically, the zygotes of elderly patients undergoing nuclear transfer are to be destroyed. Another disadvantage of pronuclear transfer is the higher risk of micromanipulation compared to spindle transfer. Due to the size of the nucleus, the use of a biopsy pipette with a larger diameter ratio may pose a risk. But with a well-optimized protocol, this risk could be eliminated. The main advantage of pronuclear transfer over spindle transfer is that the nuclei are more visible with thermo-microscopy than spindles. The most serious risk of spindle transfer is that the quality of spindle imaging may be poor and that an ICSI procedure, which is an additional micromanipulation procedure, has to be performed after the spindle transfer. This procedure is also more financially costly compared to the pronuclear procedure. In this sense, a more appropriate legal structure needs to be established in nations, and this technique needs to be further developed through further studies. It would be highly beneficial if legal platforms and ethics committees could ensure that this technique can be used clinically as an appropriate method. The fact that the technique poses no risk of micromanipulation, that the resulting children do not carry any risk of mitochondrial mutations, and that the high blastocyst rate indicates that the technique may provide a significant social advantage in the future.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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Global Regulatory and Clinical Overview of Mitochondrial Replacement Techniques in 2023

Uliana Dorofeyeva

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ABSTRACT

Mitochondrial replacement techniques offer a solution for women at risk of passing on mitochondrial disorders or experiencing infertility. Globally, the regulation of MRT is inconsistent and mostly banned, with the exception of the United Kingdom and Australia in preventing transmission of mitochondrial disorders. The regulatory landscape is constantly changing, and this review aims to explore the status of MRT in select countries as of 2023, including the UK, Australia, the United States, Singapore, Mexico, Ukraine, Greece and Albania.

KEYWORDS: Mitochondrial Replacement Therapy, Pronuclear Transfer Technique, Spindle Transfer Technique, Assisted Reproductive Technique, In Vitro Fertilization.

MANUSCRIPT

Introduction

Mitochondrial replacement techniques (MRTs) offer a solution for women at risk of passing on mitochondrial disorders to their children. Additionally, MRTs may serve as an effective technique in overcoming infertility in certain cases, particularly for older women, or women whose embryos developmentally arrest.

MRT can be performed in a number of ways, including pronuclear transfer (PNT) and maternal spindle transfer (MST). In all cases, MRT results in the transfer of the patient's nuclear DNA to an enucleated donor egg containing healthy donor mitochondria, which itself contains mitochondrial DNA. This process, creating a "three-parent" embryo, has raised regulatory concerns as it constitutes human genome modification, leading to the prohibition of MRT in many countries worldwide.

Global regulatory standing on MRT

The United Kingdom

In 2015, The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 came into effect, to allow MST and PNT to licensed clinics only when "there is a particular risk that any embryo created by the fertilisation of eggs...may have mitochondrial abnormalities caused by mitochondrial DNA." The Newcastle Fertility Centre was the first to obtain the license, with the first cases approved in 2018 and first births reported in 2023 with the trial still ongoing[(1, 2)].

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Australia

In 2022, Australia passed the Mitochondrial Donation Law Reform Bill, also known as Maeve's Law, named after a child with Leigh syndrome. A clinic that wishes to practice MRT must hold a mitochondrial donation license from the National Health and Medical Research Council Licensing Committee, which "must be satisfied that there is a particular risk of the woman's offspring inheriting mitochondria from the woman that would predispose the offspring to mitochondrial disease"[3, 4].

Before MRT can be offered throughout the country, a clinical trial must first take place. In 2023, the government awarded a $15 million grant to Monash University for the five-year mitoHOPE pilot program, which will be based in Melbourne in collaboration with Monash IVF[5].

The United States

A 2015 US law to ban gene editing of human embryos was originally included in an annual budget bill to fund government programs. Section 749 of the Consolidated Appropriation Act of 2016 prevents the FDA from using its funding or evaluating any "research in which a human embryo is intentionally created or modified to include heritable genetic modification," which has been interpreted by the FDA to include MRT. In 2019, the ban was dropped but was ultimately reinserted after a subcommittee vote, and MRT remains effectively banned in the US to this day[6, 7, 8].

The world's first MRT baby was born in 2016 in an effort led by New York-based Dr. John Zhang, whose team at New Hope Fertility Center created the embryos in the US and then sent them to Mexico to be transferred to circumvent US law. The baby's mother had the inheritable mitochondrial disease Leigh syndrome[9].

Singapore

The Bioethics Advisory Committee (BAC) of Singapore released a consultation paper in 2018 on the use of MRT and sought the opinion of the public. In 2021, the BAC released an interim report on their position on whether or not MRT should be permitted in Singapore. Due to the international and scientific status of MRT at the time, "the BAC is of the view that it is premature at the present time to consider the acceptability of clinical application of [MRT], and in vivo research performed in human subjects in Singapore for the purpose of developing [MRT]." The BAC recommends waiting for evidence of safety and efficacy from reputable international initiatives, such as the UK's Newcastle Fertility Centre, before considering MRT for severe mitochondrial disorders[10].

Mexico

Mexico has no specific federal laws or regulations regarding assisted reproduction, but MRT clinical research is permitted for unresolved infertility issues under certain regulations. Some Mexican states prohibit PNT due to local laws protecting life at the moment of fertilization[11].

Ukraine

Ukraine has no specific regulations for MRT. In 2017, the first baby was born using PNT to overcome infertility, and not for a mitochondrial disorder, at the Nadiya Clinic for Reproductive Medicine. Ukrainian clinics were a very popular location for medical tourism to bypass laws on the use of MRT in other countries, however this location is currently on hold due to armed conflict with Russia[12].

Greece

In 2019, the first baby was born by MST to overcome infertility at the Institute of Life in Greece, in collaboration with Spanish, UK and US researchers. This birth was part of a pilot study established in 2018, that recruited 25 women with infertility due to poor egg quality to undergo MST. The results of the study were published in early 2023, which reported on the births of 6 healthy babies using the technique. One child had undergone "reversal," in which some cells showed as much as 50% maternal mitochondria. While the patient didn't have a mitochondrial disorder, this raises concerns for those who undergo the process as a treatment for mitochondrial disease[13, 14].

Albania

The regulation of MRT in Albania is insufficient, with ambiguity regarding the definition of genome modification within the Oviedo Convention. Law 8876/2002 on Reproductive Health guides the use of assisted reproduction but falls short in adequately addressing the reproductive use of MRT in the country[15].

Conclusion

As of early 2023, the only two countries that have implemented measures to authorize MRT in order to prevent the transmission of mitochondrial disorders are the UK and Australia. Numerous countries prohibit MRT, either explicitly or indirectly through their stance on germline editing. Consequently, women who are seeking infertility treatment have limited choices for accessing MRT, and they often have to consider countries where it is unregulated, such as Ukraine, Greece and Albania. In these countries, MRT is considered experimental and the use of this technique requires patient consent.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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Intraovarian platelet-rich plasma injection in poor responders

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ABSTRACT

Objective:

To evaluate if it possible to improve ovarian reserve parameters and oocyte retrieval in poor responders who undergo intraovarian injection of platelet-rich plasma (PRP).

Design:

Prospective cohort study. We included 148 poor responders who underwent PRP injection between October 2021 and December 2022 in our institution, comparing pre and post PRP ovarian function. In addition, the IVF outcomes of a subgroup of patients was studied after the intervention in contrast with the previous treatment.

Results:

An improvement in ovarian reserve was observed in relation to previous values: FSH (13,57 vs. 11,32, p=0,11), AMH (0,39 vs. 0,48, p=0,06), antral follicle count (3,98 vs. 5,75, p<0,001); as well as a higher number of oocytes retrieved (2,63 vs. 3,65, p=0,01) and produced embryos (1,64 vs. 2,22, p=0,03); without a great impact on pregnancy rates.

Conclusions:

Although experimental, intraovarian PRP could restore ovarian function and be postulated as an alternative to oocyte donation in patients with low ovarian reserve who do not accept this treatment. There is a lack of randomized controlled trials to support these findings.

KEYWORDS: Ovarian rejuvenation, oocyte activation, ovarian function, oocyte donation, IVF, pregnancy.

MANUSCRIPT

Introduction

Ovarian failure due to ovarian aging in women of advanced reproductive age is one of the main causes of infertility around the world [1]. It involves a decrease in both quantity and quality of oocytes, with the consequent compromise in assisted reproduction treatment outcomes, in terms of low fertilization and blastulation rates and high aneuploidy rates [2]. There is also a reduction in ovarian volume, with increased fibrosis and loss of ovarian structure[3].

The so-called "poor responders", defined by a combination of decreased ovarian reserve parameters

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and low oocyte retrieval after ovarian stimulation, have accelerated ovarian aging[4]. This population represents 9-24% of patients undergoing in vitro fertilization (IVF), which means that up to one in four patients will have a poor reproductive prognosis[5,6].

Recently, although different approaches have been introduced to improve this prognosis, there is still a lack of effective strategies available. Within an experimental framework, in order to promote follicle activation and increase the number of retrieved oocytes, ovarian fragmentation with or without in vitro activation (drug-free IVA) and subsequent autologous transplantation[7]; as well as autologous ovarian stem cell transplantation[8], have been described. These techniques are both invasive and not yet included in randomized trials.

Interest in this subject has arisen from the observation of residual follicles on ovarian cortex biopsies from patients with primary ovarian insufficiency (POI)[9]; as well as the possibility of reactivating "quiescent" or “dormant” follicles which resulted in pregnancies through in vitro ovarian activation (IVA technique) by the incubation with PTEN (tensin-homologous phosphatase) and PI3K (phosphatidylinositol 3-kinase) inhibitors, and AKT (serine/threonine protein kinase 1) stimulants[10].

Along the same lines, a much less invasive procedure being researched, is the intraovarian injection of platelet-rich plasma (PRP). This is a concentrate derived from centrifuged whole blood that contains up to seven times more platelets than those in circulating plasma, and its regenerative properties are due to its high concentrations of growth factors such as: TGF-β (transforming growth factor-β), IGF-1 and IGF-2 (insulin-like growth factors 1 and 2), VEGF (vascular endothelial growth factor), EGF (epidermal growth factor), bFGF (basic fibroblast growth factor) and HGF (hepatocyte growth factor)[11]. Several of these factors promote tissue healing and regeneration by inducing chemotaxis, cell migration and differentiation. In addition, they contribute to angiogenesis and inflammatory changes that play a key role in tissue repair and regeneration[12,13].

It has been suggested that PRP has the potential to delay follicle atresia and oocyte degeneration [11], as well as to promote the development of primordial and primary follicles up to the pre-antral stage[14]. Another benefit is that, due to its autologous nature, it has no risk of transmissible diseases and immune rejection[15].

Numerous studies demonstrate a restoration of ovarian function in women with diminished ovarian reserve 2 or 3 months after PRP injection[4,11,16-18]; as well as an improvement of the ovarian reserve parameters (decrease in FSH[11,17], increase in AMH[11,16,19,20] and an increase in antral follicle count[4,11,19,20]). Furthermore, an increase in the number of retrieval oocytes and produced embryos after ovarian stimulation has also been reported. There have also been numerous pregnancies and live births after the application of this technique[18].

The aim of the present study was to describe ovarian reserve parameters and IVF outcomes in a cohort of 148 poor responders treated with intraovarian injection of autologous PRP.

We hypothesized that intraovarian injection of PRP may improve ovarian reserve parameters and oocyte retrieval in poor responders undergoing an assisted reproductive treatment.

Material and Method

Study design and patient selection

Prospective observational cohort study of ovarian reserve parameters and IVF outcomes in poor responders after intraovarian injection of autologous PRP. This study was conducted at the Reproductive Medicine Center "Procrearte", Buenos Aires, Argentina, from October 2021 to December 2022.

148 patients under 45 years old were included, all of whom had previously undergone at least one assisted fertilization treatment with a recovery of less than 5 oocytes and/or a low ovarian reserve profile (Poseidon 1, 2, 3 and 4). Low ovarian reserve was defined as: AMH <1 ng/ml and/or early follicular phase antral follicle count <5.

Patients with oncological disease, history of chemo- or radiotherapy, severe cardiac disease, ovarian and/or deep endometriosis, polycystic ovarian disease, active sexually transmitted disease, multiple previous pelvic surgeries, platelet function disorder, moderate or severe thrombocytopenia, coagulopathy and anticoagulant treatment were excluded.

Ovarian function was performed in each patient through hormonal assays (FSH, LH, oestradiol and AMH) and total antral follicle count, in order to compare the previous values (within 6 months before the PRP injection) with those at 3 months post-procedure. In addition, for patients who underwent ART, we compared the number of oocytes retrieved, the number of MII oocytes, the fertilization rate, the number of 2 pronuclear and total produced embryos after PRP injection with respect to the last treatment preceding this therapy. Spontaneous and post-ART pregnancies were recorded up to the time of conclusion of this study.

All participants signed an informed consent form for the procedure, which explained the experimental approach, as well as the possible associated risks.

Patients who chose to participate returned a signed copy of the form to the clinic.

Procedures

For each patient, 60 ml of blood was obtained under sterile conditions from the median antebrachial vein two hours before the intraovarian injection. All patients were instructed not to take aspirin for 7 days prior to the procedure and fasted for a minimum period of 6 hours.

The blood was placed in two sterile 50 ml tubes with 7.5 ml ACD-A (anticoagulant solution dextrose citrate) (ratio 1 vol ACD-A: 4 vol blood). Double centrifugation was performed at 2000 and 2500 rpm, for 6 and 10 minutes respectively. The platelet concentrate was suspended and homogenized in 7.5 ml of autologous plasma at a concentration of 1.5 x 10 6 /ul. In addition, 2.5 ml of physiological solution was added since dilution increases the regenerative and neovascularization effect by diluting growth factors that inhibit this function. The suspension was then placed in a refrigerator at 4°C for 30 minutes and activated with 22-25 mL CaCl2 at 10%, i.e. for 10 mL, 1 mL of CaCl2 was added. PRP preparation was performed in a restricted access area, under aseptic conditions and using a laminar flow hood.

Before the intervention, an assessment of the clinical status of the patients was carried out with a complete blood hemogram, coagulogram, monitoring of renal function, electrocardiogram and serologies (VIH, hepatitis B, hepatitis C, syphilis). In addition, ovarian reserve parameters were evaluated with hormonal profile (FSH, LH, estradiol and AMH) and transvaginal ultrasound with antral follicle count between the second and fourth day of the menstrual cycle.

PRP injection was performed in all cases at least 2 months after the last failed fertility treatment, at the follicular phase (day 7 to 10 of the menstrual cycle). The patient was prepared according to our institution's ovarian aspiration puncture protocol, in a dorsal lithotomy under local anesthesia or neurolept anesthesia. Firstly, both ovaries were visualized by transvaginal ultrasound, accessing the central portion of the ovaries through a 17 gauge 30 cm length Cook® single lumen needle. Subsequently, gradual infusion was performed in the subcortical and stromal area, using 3 mL of activated PRP per ovary, through a 5 ml syringe connected to the silicone plug of the needle. Although the ovaries of elderly maternal age and poor responders may be small and fibrotic, injection was achieved by creating new planes through distension and injection at multiple sites. The maximum time taken was 20 minutes.

After the procedure, patients were taken to the recovery room and discharged the same day after an initial examination period of 30-40 minutes. Antibiotic prophylaxis was indicated according to our institution's follicular ovarian puncture protocol. After the operation, the pelvis was thoroughly examined by ultrasound, in order to check total vascular integrity. The supine position was recommended for 15 minutes after the infusion.

During the third month after injection, ovarian function was monitored by hormone profile (FSH, LH, estradiol and AMH) and antral follicle count by transvaginal ultrasound, between the 2nd and 5th days of the menstrual cycle.

According to the patient's response (at least three antral follicles visualized by transvaginal ultrasound) and the couple's preferences, ART was initiated in the third menstrual cycle after the procedure, using a protocol with gonadotropin-releasing hormone (GnRH) antagonists and 300 IU of gonadotropins (follitropin alfa and/or human menopausal gonadotropin) from day 2 of the cycle. We prescribed a GnRH antagonist once the follicle diameter reached 14 mm and/or estradiol levels were at 300-400 pg/ml. Ovulation was triggered with recombinant human chorionic gonadotropin when follicles reached 18 mm. Oocyte retrieval was performed 36 hours after discharge and then oocytes were inseminated by intracytoplasmic sperm injection (ICSI).

The embryo transfer was performed in the operating room under transabdominal ultrasound guidance following the usual protocols of the procedure, between days 3 to 6 post puncture, according to medical criteria. Luteal phase support consisted of vaginal micronized progesterone (600 mg daily), until quantitative human chorionic gonadotropin (hCG) tests were obtained fourteen days after embryo transfer.

The cryopreserved embryo transfer cycles were all artificial, and included the indication of oral oestrogens and vaginal progesterone.

Statistical analysis

Quantitative variables were described by mean and standard deviation. Differences in quantitative variables between groups were compared by t-test and qualitative variables by chi-square test. Statistically significant differences were considered for those probabilities less than 0.05.

Statistical analysis was performed with Epi Info 7.2.5.0 software.

Outomes

The 148 patients included in the study had an average age of 39.61 years (33-44). At the time of the procedure, they had undergone 1 to 6 ovarian stimulations for ART (mean 1.63). Regarding ovarian function, an improvement in AMH, FSH and antral follicle count was obtained after PRP injection. This last parameter was statistically significant (**table 1**).

	Before PRP	After PRP	ρ
FSH (mUI/mL)	13,57 ± 8,94	11,32 ± 7,45	0,11
LH (mUI/mL)	6,61 ± 3,09	7,36± 6,51	0,41
Estradiol (pg/mL)	77,17 ± 103,59	78,26 ± 76,36	0,93
AMH (ng/mL)	0,39 ± 0,33	0,48 ± 0,39	0,06
Antral follicle count	3,98 ± 2,29	5,75 ± 2,82	**<0,001**

Table 1. Ovarian reserve before and after PRP treatment.

A subanalysis of the outcomes was performed according to different age ranges categorized as group 1 (under 40 years), group 2 (40-42 years) and group 3 (over 42 years). The significant improvement in antral follicle count was only persistent in groups 1 (6.04 vs. 4.38; p=0.01) and 2 (6 vs. 3.5; p=0.001), but not in those over 42 years of age (4.94 vs. 3.87; p=0.11). The corresponding AMH values for each group were 0.49 vs. 0.52, p=0.17; 0.44 vs. 0.47, p=0.64; and 0.32 vs. 0.42, p=0.14; respectively.

At the time of finalization of this study 97 ARTs had been performed, all of which were indicated at the third cycle post intra-ovarian PRP injection. Of the initial 148 patients, there was a loss in follow-up of 9.45% (14 cases); and 6 spontaneous pregnancies (4.05%) were noticed between 2- and 8-months post therapy, 5 of which were ongoing pregnancies and 1 culminated in miscarriage.

Of the remaining 128 patients, 31 finally decided not to undergo treatment with their own oocytes. Oocyte vitrification was performed for maternity postponement in 13 of the remaining 97 cases. Thus, of the initial sample, 84 patients underwent ART for reproductive purposes. We registered 10 post-IVF pregnancies (10/84=11.91%), of which 7 were ongoing (1 twin), 1 live birth, 1 ectopic pregnancy and 1 miscarriage (at week 9 of gestational age).

There were 10 cases of ovarian stimulation failure (11.91%), which did not undergo follicular aspiration puncture. There were 7 patients (8.33%) without oocyte retrieval (9.52%), 3 with immature oocytes (3.57%), 6 cases of fertilization failure (7.14%), 7 arrested embryos (8.33%), and 12 patients (14.28%) who underwent preimplantation genetic testing for aneuploidy (PGT-A) resulting in aneuploid (10 cases) or arrested embryos (2 cases).

Therefore, out of the total sample, only 39 patients were suitable for embryo transfer. Six had not yet undergone it. One patient performed a fresh embryo transfer, followed by a cryopreserved one. In 64.71% of the cases a single embryo was transferred, while in 35.29%, 2 embryos were transferred. A total of 67.65% of the transfers corresponded to embryos at 120 or 144 hours of development.

The pregnancy rate in the group of patients who transferred at least one embryo was 29.41% (10/34), consisting of 4 positive after embryo transfers (4/19) and 6 positive after cryopreserved ones (6/15). Currently, there are 7 ongoing pregnancies, 2 live births and 1 ectopic pregnancy.

A subgroup of 20 patients underwent pre-implantation genetic testing for aneuploidy (PGT-A) and had 26 suitable embryos on day 5 of development. Nine of them were euploid (34.6%) and 17 were aneuploid (65.35%).

An analysis of the 97 ART cases was performed, comparing the outcomes after PRP injection with the last treatment prior to PRP in each case. The average age of these patients was 39.28 years (33-44). In this group, a significant improvement in ovarian reserve was observed with respect to previous values (assessed by AMH and antral follicle count); as well as better results in number of oocytes retrieved, number of mature oocytes (MII), number of 2 pronuclei and evolved embryos; compared to the cycle prior to the therapy. There was no difference in the fertilization rate between the two groups (**table 2**).

No complications or adverse effects were recorded in the cases performed during the period of this study.

Descriptively, patients who achieved pregnancy had a mean age of 38.18 years (35-43), AMH of 0.56

ng/ml (0.02-0.71) and antral follicle count of 3.33 (0-6) prior to intraovarian PRP therapy.

	Before PRP	After PRP	p
FSH (mUI/mL)	13,71 ± 9,11	10,64 ± 4,81	0,06
LH (mUI/mL)	6,41 ± 3,21	6,17 ± 3,21	0,75
Estradiol (pg/mL)	60,68 ± 58,02	49,72 ± 21,86	0,25
AMH (ng/mL)	0,46 ± 0,29	0,62 ± 0,36	**0,03**
Antral follicle count	4,5 ± 2,09	6,15 ± 2,58	**<0,001**
Number of retrieved oocytes	2,63 ± 2,42	3,65 ± 3,17	**0,01**
MII oocytes	2,17 ± 2,07	3,09 ± 3,06	**0,01**
Number of inseminated oocytes	2,34 ± 2,27	3,46 ± 3,13	**0,01**
Number of 2 pronuclei embryos	1,62 ± 1,81	2,31 ± 2,08	**0,02**
Fertilization rate	(1,62/2,34) 69,23%	(2,31/3,46) 66,76%	0,77
Number of abnormal fertilized embryos	0,16 ± 0,42	0,25 ± 0,65	0,41
Number of produced embryos	1,64 ± 1,84	2,22 ± 2,07	**0,03**
Number of evolved embryos	0,78 ± 0,89	1,46 ± 1,27	**0,01**

Table 2. Outomes.

Discussion

Intraovarian PRP injection was recently introduced as an alternative to egg donation in patients with poor reproductive prognosis[22].

Regarding its mechanism of action, two hypotheses are proposed: the more controversial one introduces the concept of neo-oogenesis, suggesting the presence of ovarian stem cells as a source of oocytes in adult ovaries [23]. Numerous studies have shown that it is possible to obtain mitotically active germ cells from healthy adult ovarian tissue in mice and humans [24,25]; however, there is no evidence that spontaneous stem cell reactivation occurs naturally in the adult human ovary. Another possible explanation is that PRP could activate the development and maturation of "dormant" or quiescent primordial follicles, increasing the pool of ovulatory follicles[23].

PRP-derived growth factors include multiple regulatory proteins that bind to cell membrane receptors and direct important chemical messages. Through this interaction, they trigger inter- and intracellular signalling mechanisms that direct growth, proliferation and differentiation of cells[22]. Unlike hormones, PRP growth factors act only in the proximity of their release site, playing an important role in the restoration of the ovarian niche, mainly by promoting physiological processes of angiogenesis, proliferation and growth, apoptosis, control of inflammation and cell migration[26-29].

In the last decade, numerous studies have reported that injecting plasma directly into the ovary increases folliculogenesis and restores ovarian function and hormonal profile, with a consequent improvement in oocyte retrieval in patients undergoing ART[19]. The first results were reported by Pantos et al., who demonstrated the possibility of restoration of ovarian function in a cohort of eight perimenopausal women undergoing IVF, with successful oocyte retrieval [30].

In this study we investigated whether intraovarian injection of PRP improves ovarian reserve and IVF outcomes in poor responders. The decision to initiate ovarian stimulation protocol 3 cycles after the procedure was based on the knowledge that follicular development takes an average of 90-120 days from primordial follicle recruitment to antral follicle development, supporting the hypothesis that PRP could stimulate the development of pre-antral follicles and delay atresia.

We demonstrated an improvement in ovarian function in these patients by a decrease in FSH values and an increase in both AMH and the number of antral

follicles. These findings are similar to those reported by a recent study of 510 poor responders, in which hormone values and antral follicle counts were compared before and after PRP injection, resulting in a decrease in FSH (20.6 IU/ml vs. 16.4 IU/ml; p<0.001), and an increase in AMH (0.35 ng/ml vs. 0.53 ng/ml; p<0.001) and antral follicle count (2.6 vs. 4.2; p<0.001)[4]. The same study also evaluated the impact of different variables on the outcomes and considered 40 years old as a cut-off age for patients who would not benefit from PRP due to failure of ovarian response (sensitivity of 61.54% and specificity of 73.77%). In our study, all patients had an increase in antral follicle count after the procedure; however, this parameter only had a significant impact in patients up to 42 years of age.

A prospective non-randomized controlled trial in which 46 patients with diminished ovarian reserve who underwent PRP injection (study group) versus 37 who did not (control group), showed at 3-month follow-up a significant improvement in FSH, AMH and antral follicle count in the study group, while there was no change in the control group [11]. What is interesting about this study, although it was not randomized, is that it had a control group. Similar findings have been reported by other researchers[17,19,20,31,32].

A recently published study that evaluated the impact on a cohort of 80 women with diminished ovarian reserve or poor responders failed to demonstrate a statistically significant benefit following intra-ovarian PRP. The authors concluded that one of the possible explanations may be due to the inclusion of women with poorer reproductive prognosis, especially in terms of advanced age, and therefore are inclined to infer that the potential effects are still being researched and that these outcomes should be interpreted with caution. So far they have reported two pregnancies in patients in their 40s with several failed fertility treatments[33].

Regarding ART outcomes, we demonstrated a significant improvement in the number of retrieved oocytes, number of metaphase II oocytes, number of 2 pronuclei and developing embryos, with respect to the cycle prior to PRP application. There were no differences in fertilization rates. Likewise, Cakiroglu et al. obtained a significant increase in the number of retrieved oocytes (2.2 vs. 3.4; p<0.001), number of metaphase II oocytes (1.7 vs. 2.7; p<0.001), fertilization rate (57.6 vs. 66.9; p 0.008) and number of 2 pronuclei embryos (1.3 vs. 2.1; p<0.001) [4]. Other studies also reported an improvement in assisted fertilization parameters as well as a decrease in cancellation rates[19,31,34].

The pregnancy rate in our total sample was low. However, it is important to note that if only patients under 40 years of age are included, the pregnancy rate is 27.5% (11/40), compared to 11.36% (5/44) in the older population. According to a retrospective cohort study that analyzed more than 26,000 IVF/ICSI cycles, the cumulative pregnancy rate after a complete IVF cycle was 14.73% for patients included in the Poseidon 3 group, and 6.73% for the Poseidon 4[35]. Our study is still in the follow-up period, and a percentage of patients have cryopreserved embryos that have not yet been transferred, so no results are reported in cumulative pregnancy rate, nor in subsequent ovarian simulations.

Although ART outcomes were better after PRP therapy, we cannot infer an improvement in oocyte quality or demonstrate a real impact of the number of retrieved oocytes and produced embryos on the pregnancy rates. The low number of patients who underwent PGT-A does not allow us to demonstrate a benefit of intraovarian PRP on aneuploidy rates. To date, only one pilot study that included 12 patients has been published, comparing PGT-A results of the cycle following PRP treatment, against those of the previous one. The embryo euploidy rates were 8.11 vs. 39.28%, respectively. Although the sample size was very low, they attributed the findings to the local paracrine effect that plasma growth factors may exhibit, correcting meiotic aberrations in human oocytes, directly impacting the rate of euploidy[21].

It is unknown what influence the mechanical stimulation produced by ovarian puncture has on the pool of quiescent follicles, and therefore its contribution to the published outcomes. Currently, there is an ongoing prospective randomized study which will compare the results after ovarian PRP with the injection of a platelet-poor plasma fraction (Registration # NCT04278313)[33].

One of the strengths of this study is its prospective design as well as the unified protocol that we have implemented, with PRP preparation 2 hours before the procedure, performed by the same operator. At the same time, we highlight the comparative design, which allowed the same cohort of patients to be included as their control group, thus monitoring differences in demographic variables.

One of the main limitations is the short follow-up period, as we only evaluated the outcome of the first IVF, ignoring the long-term consequences and the cumulative pregnancy rates. On the other hand, we did not have a control group, but each patient was her own control, which is not ideal given the possible regression to the mean in the obtained results. Other limitations were the inclusion of patients with a very poor prognosis and mostly aged, a wide age range, and a high percentage of patients lost to follow-up due to the prospective nature of the study.

Finally, it is important to emphasize that there is a wide heterogeneity on the protocols of this technique, with regard to multiple factors such as: the volume of processed blood, the volume of injected plasma, the method of platelet activation, the plasma injection route, the best timing of the cycle for its application, the number of infusions to be performed, the follow-up time, the time interval until ART, the definition of poor responders. Furthermore, actual evidence is based on a few series of cases, or on prospective controlled and uncontrolled pilot studies, all of which are not randomized. For these reasons, we believe that this technique should be considered experimental and that it is crucial to identify the target patients that could benefit from it, according to different variables.

Conclusion

Intraovarian PRP had a favorable impact on ART outcomes 3 months after injection compared to the previous cycle. There was an improvement in ovarian reserve, with a limited impact on pregnancy rates. Further randomized controlled trials are required to validate our findings.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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Surrogacy Unveiled: Doctors Experience and Stories of Hope and Challenges

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ABSTRACT

Objective

To focus on the experiences of doctor's, intending parents, and surrogates with beautiful surrogate babies, including legal issues and the challenges posed by the pandemic.

Study Design

This study adopts a novel strategy by investigating surrogacy from a medical professional's viewpoint. We want to offer our knowledge and wisdom gained from dealing with surrogacy as a doctor, especially in light of the many challenges brought on, including the COVID-19 pandemic. The purpose of this study is to comprehend the role of the doctor in surrogacy and how it relates to intended parents' and surrogate moms' experiences.

Subjects

This study's subjects include the doctor, who is also its principal investigator, as well as intending couple and surrogate mother. While intending parents and surrogate moms contribute further insights into their involvement in the surrogacy process, the doctor's experiences serve as the central narrative.

Main Outcome Measures

In this study we have looked into indications, neonatal outcomes, legal aspects, in house development, management during covid 19 pandemic of all surrogates through our experience at a single center over 5 years.

Results

This study provides insight into the experiences of couples considering surrogacy, the effective management of surrogates during a pandemic, and the impact of surrogacy on the developmental outcomes of children.

Conclusions

The findings highlight the experiences of intending couples during the challenging period of the COVID-19 pandemic, emphasizing prolonged separations, varying perceptions of baby development, and increased anxiety. The successful handling of surrogates

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in this context, where 19 out of 54 tested positive for COVID-19 but all recovered, underscores the adaptability and success of established protocols. Additionally, the positive developmental progress in children and the prevalence of donor eggs in surrogacy outcomes contribute to a comprehensive understanding of surrogacy. Overall, this study sheds light on the emotional, physiological, and developmental aspects of surrogacy.

KEYWORDS: Legal, Foreign Surrogacy, Intending parents, Infertility.

MANUSCRIPT

Introduction

The term "surrogate" is derived from the Latin word "Subrogare," signifying "to substitute," suggesting an individual appointed to act in the place of another. In this context, a surrogate mother is a woman who becomes pregnant and carries a child with the intention of relinquishing the child to another person or couple, often known as the "intended" or "commissioning" parents. Surrogacy is an essential fertility treatment, particularly for women unable to conceive due to the absence of a uterus, uterine anomalies, severe medical conditions, or other reasons prohibiting pregnancy. It allows these individuals to achieve motherhood by using an embryo created by themselves or using gametes from a donor, which is then transferred to the uterus of a gestational carrier. Furthermore, this technique facilitates gay couples and single men to attain fatherhood by creating an embryo with their sperm and donor oocytes.[2]

Countries	Legal Status
South Africa	Altruistic surrogacy is allowed only for residents, with no financial rewards for surrogate mothers. beyond pregnancy-related expenses.
Nigeria	Lack of legal framework for surrogacy in Nigeria. Practice tolerated in certain regions. Questionable legitimacy due to absence of laws or judicial rulings.
Japan	Absence of surrogacy legislation. Use of guidelines and legal opinions. Societal and cultural factors contribute to stigmatization and discouragement.
Thailand	Exclusive allowance for opposite-sex married couples. Requirement for couples to be Thai residents. Limited to commercial surrogacy contract arrangements.
China	Illegal, yet widespread and tolerated.
India	Altruistic surrogacy is legal.
Israel	Legal with state approval.
Australia	Altruistic surrogacy legality across jurisdictions except Northern Territory. Commercial surrogacy classified as a criminal offense.
Canada	Altruistic surrogacy is legal.
United States	Lack of federal surrogacy law in the United States. Varied regulations at the state level.

Table-1. Status of surrogacy of some countries [4]

Over the past two decades, this decision opened the doors for Indian citizens and international singles or couples from various corners of the world to explore various assisted reproductive technologies, including egg donation, in vitro fertilization (IVF), and surrogacy. This legal framework laid the foundation for India's growing role in the global surrogacy industry. Then, on January 23, 2022, the Surrogacy Act came into effect, bringing with it a new set of regulations and guidelines governing surrogacy arrangements in the country. These changes marked an important development in the field of surrogacy in India.[3]

Surrogacy can be categorized into two types: traditional and gestational. Traditional surrogacy involves artificial insemination with the intended father's sperm, making the surrogate mother a genetic parent along with the intended father. In contrast, gestational surrogacy, also known as host surrogacy, entails transferring an embryo from the intended parents or using donated gametes to the surrogate's uterus. In gestational surrogacy, the woman carrying the child has no genetic connection to the baby.

Additionally, surrogacy arrangements fall into two broad categories: commercial and altruistic. Commercial surrogacy involves monetary compensation for the surrogate mother's services, while altruistic surrogacy only allows reimbursement for medical and pregnancy-related expenses, along with insurance coverage [2].

Within the realm of assisted reproductive technologies and surrogacy, the concept of "in-house surrogacy" has gained recognition. This innovative approach entails the surrogate mothers voluntarily residing within the hospital premises during the pregnancy and birthing process. It offers benefits such as enhanced medical supervision, medical and emotional support, reduced travel, increased accessibility, personalized pregnancy care, minimized legal and ethical concerns, family-centered care, comprehensive birth and postpartum care, improved psychological well-being, and optimized birth planning.

Foreign Surrogacy

Countries where gestational, commercial, and international surrogacy are legal include Russia, Ukraine, Greece, the UK, and Iran. We have delivered nearly 383 babies for foreign couples.

Commercial surrogacy was permitted in India for foreigners starting in 2002. Foreigners have traditionally found India to be a welcoming and satisfying destination for surrogacy. Our hospital has hosted individuals from over 48 different countries who sought surrogacy services here. The happiness and contentment of these individuals were palpable, so much so that some of them chose to give Indian names to their children born through surrogacy like Krishna, India, Arjun, Ram, Anand, etc. Their satisfaction extended beyond the birth, as many of them continue to support the surrogates who played a vital role in this journey by sponsoring their children's education and providing essential needs. We also maintain connections with our patients, with some of them sharing photos of their surrogacy-born babies and updating us on the children's well-being.

However, with provisions in the draft ART Bill of 2014 and a notification from the Health Ministry of India on November 3, 2015, surrogacy became prohibited for foreign nationals, including OCIs and PIOs.[8]

Indication of surrogacy

When a pregnancy is confirmed in the gestational carrier, she may either stay at the surrogate house or at her own home, depending on the surrogate’s choice. The concept of the surrogate house has garnered significant attention in recent times due to various factors. It was established to address the wishes of many surrogates who seek shelter during their pregnancy. This need arises because many surrogates wish to keep their surrogacy confidential from friends and family, especially in rural areas where there may be a lack of awareness about the scientific procedures involved in surrogacy.

The surrogate house serves as a residence for the surrogate throughout her entire antenatal period, up to the delivery date, providing for all her medical and personal needs. Given the importance of the pregnancy, the obstetric care provided to surrogates is comprehensive.

In the surrogate house at our center, surrogates are under the 24-hour supervision of nursing staff, along with a team of professionals, including a dietician, physiotherapist, counselors, and gynecologist, to ensure their medical well-being. Surrogates receive ample rest and nutritionally complete meals, which are essential for their health during pregnancy. Being under one roof, they offer each other significant emotional, moral, and psychological support. Surrogates can also meet with their families and children and stay in constant contact with them via phone. They have the flexibility to return to their homes as they wish. Furthermore, young children of surrogates can stay with them at the surrogate house during weekends and school holidays. Staying at the surrogate house is voluntary, and any surrogate wishing to stay at her own home can do so. Activities in the surrogate houses included language lessons in Gujarati, Hindi, and English for the surrogates and their children. There were also enrolled for sewing classes, lessons on pregnancy rituals, beautician courses, and creative activities such as clay

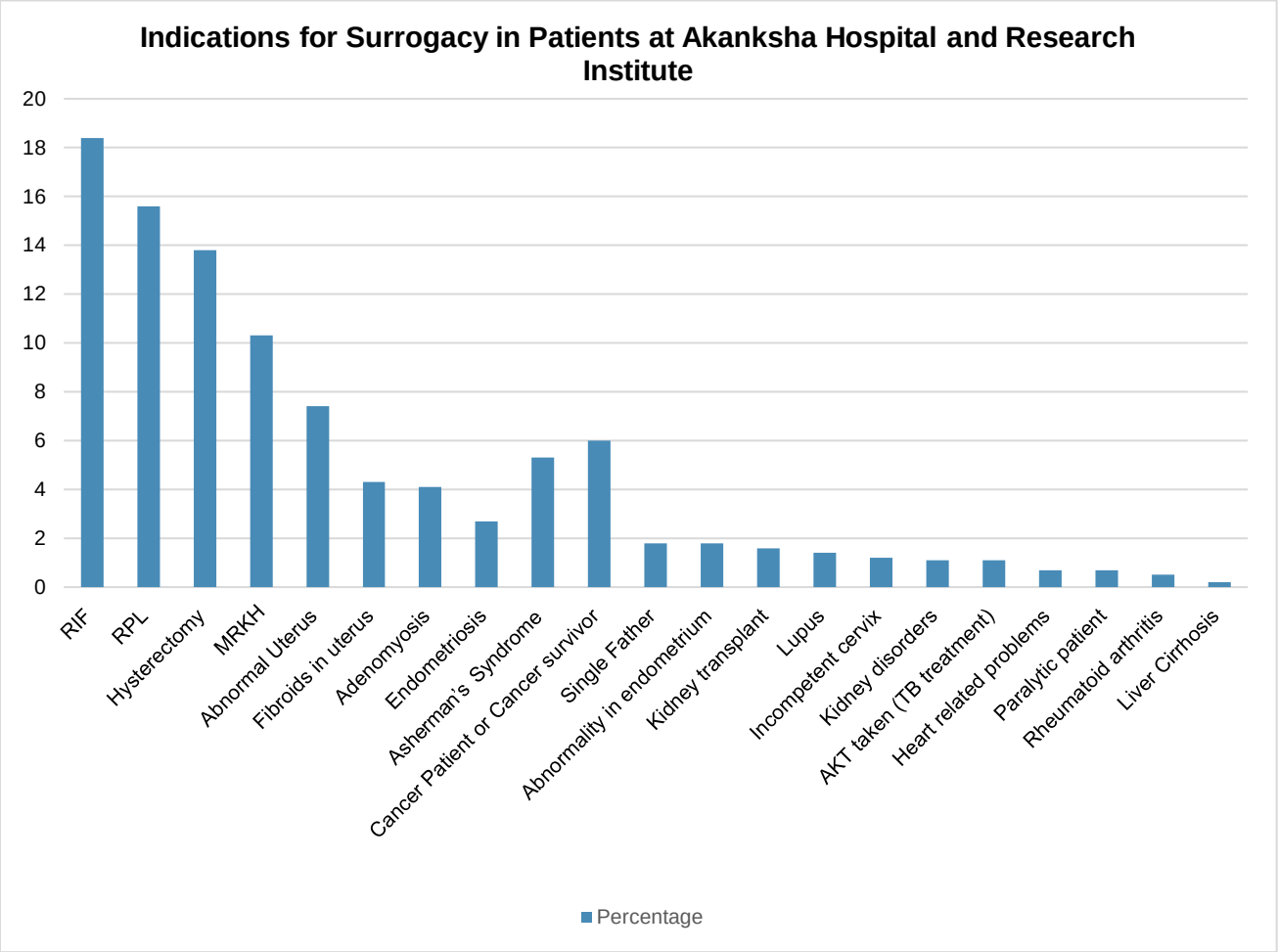

Fig-1 Represents indication for surrogacy

modeling and paper work. Additionally, yoga and exercise classes were provided to promote the health and well-being of the surrogates.

While at the surrogate house, the surrogate undergoes obstetrics assessments every 14 to 20 days until the delivery date. Obstetric scans are performed at various intervals: at 6–8 weeks, 11–13 weeks for an anomaly scan, at 20–22 weeks for a 3D–4D anomaly scan, at 28 weeks, and at 34–36 weeks for a growth scan. Any additional scans are conducted based on the obstetrics requirements. Regular updates about the surrogate's pregnancy, such as weight gain, vitals, fetal growth, antenatal investigation reports, and scans, are sent to the intended couple via e-mail.

After delivery, the surrogate is observed for a minimum of 15 days before being discharged. Her medical tests including repeat haemogram is done and she is also provided with a post partum rehabilitation kit comprising of sanitary pads, abdominal belt, haematinics and calcium tablets.

Practical Problems

The arrangement of surrogacy, being a third party method of reproduction, is a delicate one. In our experience, while majority of the cases have been uneventful and smooth, there are a few pinpointable special cases which need to be discussed. These have in-turn enhanced our learning curve in surrogacy.

Legal Issues

1. *Baby Manji Yamada vs Union of India.*

The biological parents Dr. Yuki Yamada and Dr. Ikufumi Yamada came to India from Japan in 2007 and commissioned surrogacy at Akanksha Hospital Anand, Gujarat. After transfer of their embryo into the surrogate, the mother left India due to marital discord and the couple was divorced before the baby was born. The father had to leave India as his visa was expiring and his mother stayed in Anand to take care of the baby. The baby was issued a birth certificate with her biological father's name in it. However, the baby had to be shifted to Rajasthan due to a law and order situation in Gujarat. A writ petition was filed by an NGO M/s SATYA before the High Court of Rajasthan, Jaipur

Bench against Union of India and State of Rajasthan. The writ petition challenged surrogacy and criticised it as feeding an illegal industry in India and need for the enactment of a law. The division bench passed an order to produce the child before the court. This order was challenged by the grandmother on behalf of the baby in the Supreme Court of India. A two judge bench gave the following judgement: Surrogacy is a well-known method of reproduction and elaborated on various forms of surrogacy; the petition made by the NGO Satya was not in good faith and certainly not in public interest. In the present case if any action has to be taken, it has to be the Commission constituted under Commissions for Protection of Child Rights Act, 2005. It also stated that till then no complaint had been made by anybody relating to the child and hence the writ petition was disposed with a direction that if any person has any grievance, the same can be ventilated before the Commission constituted under the Act. Also, Learned Solicitor General, stated that upon submission of relevant application, request for extension of visa for the grandmother and travel documents to the Baby shall be disposed of expeditiously. Subsequently, the regional passport office granted an 'identity certificate' to the baby and the baby flew to Japan on Japanese visa provided on humanitarian grounds. [6]

2. *Union of India vs Jan Balaz.*

This German couple was intending parents and had twin babies delivered in India through surrogacy. The birth certificate had the name of the genetic father and the surrogate mother as the parents. The father had problem getting travel document for the children and he moved the Gujarat High court which ordered for the babies to be provided with Indian passports. However, Indian Government refused to provide the children with Indian citizenship as they were born through surrogacy while the German authorities refused to grant them visa or citizenship as the state did not recognise surrogacy. Finally, the couple could go through inter-country adoption process supervised by Central Adoption Resources Agency (CARA) which took about two years for the couple to return to Germany with their children.[11]

3. *Grandmother became Surrogate mother.*

An Indian couple residing in the UK faced the challenge of finding a surrogate mother as the wife was born without a uterus. Faced with the husband's desire for a genetic child and the inability to find a suitable surrogate in Anand and India over three months, a unique solution emerged. The mother volunteered to be the surrogate for her daughter. After a 9 months, she successfully gave birth to twins, a boy and a girl, fulfilling the couple's dream of parenthood. [12,13]

The Impact of COVID-19

During the COVID-19 pandemic, India encountered an extraordinary rise in cases, prompting a nationwide lockdown from March 23 to May 30, 2020. Even after the formal cessation of the lockdown, numerous states, especially those identified as red or orange zones, sustained restrictions. These circumstances brought forth substantial challenges for intending couples trying to reach the hospital to be with their newborns.

Consequently, Akanksha Hospital and Research Institute witnessed a significant number of 46 babies admitted in the Neonatal Intensive Care Unit (NICU) during this period. The challenges faced by intending parents revolved around travel restrictions, limited accessibility due to zone designations, and the general apprehension regarding the health risks associated with the pandemic.

The hospitals infection control committee laid down strict protocols to contain all the in-house surrogates and their children in a covid free bubble. Surrogates were restricted from meeting their husbands and other relatives. They were also educated about infection control practices such as handwashing and masking up.

These stringent protocols and regulations posed constraints on the intending parents' visitation rights and interactions with their newborns. These limitations complicated the emotional and psychological well-being of the parents and affected their ability to bond with the newborns and the surrogate mothers. The situation raised notable concerns about the emotional connection, parental rights, and the mental health of both the parents and the surrogate infants during this crucial period. Such challenges emphasized the need for enhanced support systems and innovative measures to mitigate the impact of similar health crises on the intending parents and the surrogacy process.

The doctors attending the surrogates were constantly involved in counselling and reassuring the intended parents on the wellbeing of their surrogate. This situation was one of a kind, as even for the doctors, as all intended parents and the relative of the surrogates, had given the responsibility entirely to the treating doctors for the overall wellbeing of the surrogates and their unborn babies. This led to a lot of mental pressure on part of doctors.

During the COVID-19 pandemic, our hospital encountered several challenges. The first instance was when a surrogate, after visiting her home, tested positive for COVID-19. Following her diagnosis, she was transferred to isolation, but she refused to stay and returned to the hospital, leading to another surrogate contracting the virus. Both infected surrogates were

isolated within the hospital premises, receiving round-the-clock care from our staff nurses.

Subsequently, another surrogate who lived off-site was diagnosed with COVID-19 but declined to stay in the hospital's isolation ward. She and her husband requested a separate isolation house and 24-hour nurse assistance, which we provided. We conducted regular health check-ups and free COVID-19 tests for all surrogates. Daily phone calls from the families of surrogates and intending couples became a significant challenge, as their relatives tended to avoid hospital visits and entrusted the responsibility of the surrogates and their children to our hospital staff. We administered nebulizers three times a day, prepared Kadha(Ayurvedic Medicinal Drink), and provided homeopathic medicine to enhance their immune systems. Symptomatic cases were promptly tested for COVID-19.

We extended comprehensive care to the surrogate mothers' children while the newborns were under our supervision in the Neonatal Intensive Care Unit (NICU). Daily updates regarding the newborns' well-being and progress were consistently communicated to the intending couples. Our team diligently followed all precautionary measures by getting vaccinated, maintaining physical distance, wearing masks, frequent hand sanitization, and isolating individuals showing COVID-19 symptoms, ensuring the safety of all involved.

Materials and Methods

The realm of surrogacy an its various aspects explored in this research paper using a qualitative and retrospective study approach, with a focus on the perspective of a medical professional. The study is focused on the doctor's experiences with surrogacy and pays specific attention to the special difficulties brought on by the COVID-19 pandemic. The study also weaves together the individual accounts of intended parents and surrogate moms who both played crucial roles in the surrogacy process.

Data Collection

1. Author's Experience: The primary source of data is the author's extensive and multifaceted involvement in the field of surrogacy. As a medical practitioner specializing in reproductive medicine, the author has engaged in consultations, performed medical procedures, and witnessed the emotional journeys of surrogate mothers, intending parents, and newborns.

2. Intending Parents and Surrogate Accounts: To provide a more comprehensive perspective, this study incorporates firsthand accounts and narratives generously shared by intending parents and surrogate mothers who have been integral to the surrogacy process. These narratives were gathered voluntarily to ensure that the voices of those who have experienced surrogacy are included.

In our research, we addressed four fundamental aspects

1. COVID-19 Lockdown experience: To gather pertinent data, we developed a structured Google Form questionnaire, which was distributed to intending parents. This questionnaire aimed to capture their experiences during the COVID-19 lockdown, with a primary focus on their encounters during the period of separation from their newborns and the challenges faced in connecting with the surrogate mother.

2. Management of Surrogate Mothers with COVID-19: We also examined our approach to managing cases involving surrogate mothers who tested positive for COVID-19.

3. Retrospective observational study has been carried out at Akanksha Hospital on date 20/03/2023 to evaluate impact of surrogacy on child’s developmental mile stone. This study contained data of 38 children (Age group 3 year to 6 year) regarding impact of surrogacy on child’s milestone development. Data were collected in the form of questionnaire by google form sheet which were filled by either child’s parents or relatives. This questionnaire comprised of questions to assess early physical development i.e., gross/fine motor skill; personal/social communication skill; and some questionnaire of problem solving for assessment of general intelligent development.

4. Neonatal Outcome of Surrogacy- We had also conducted one study where we retrospectively analyzed 201 surrogate pregnancies and their respective births, leveraging data collected from hospital records and databases. The information encompassed details on surrogate pregnancies, birth outcomes, and the source of eggs (self or donor). Key parameters analyzed included the maturity at birth, birth weight, and classification of the egg source as either self-egg or donor-egg.

Results

COVID-19 Lockdown experience

The study also collected responses from parents who experienced the challenges posed by the COVID-

19 pandemic and its associated restrictions in their surrogacy journey. These responses shed light on various aspects of their experiences and emotions.

Duration of Separation

The duration of separation between parents and their newborns ranged widely, from as short as 5 days to as long as 2 months. These findings highlight the diverse experiences that parents faced, with some enduring more extended periods of separation.

Current Baby Development

Parents' assessments of their child's development varied. Some reported that their child's development exceeded expectations, while others described it as normal. Tragically, a car accident in which the couple with baby was travelling in one case resulted in head injury, with no developmental progress noted.

the afternoon with the couple to update about the baby's progress.

Emotions During Separation

The emotions experienced by parents during the separation period were multifaceted. The dominant emotions included anxiety, helplessness, and sadness. Other emotions such as frustration, fear of COVID-19, and relief were also reported. These findings reflect the complex and emotionally taxing nature of this period. Specially for those intended parents whose surrogates delivered in their absence and they missed the crucial moment of the birth of their baby.

The results provide valuable insights into the psychological impact of pandemic-related restrictions on intending parents, emphasizing the need for better support and coping mechanisms in similar circumstances.

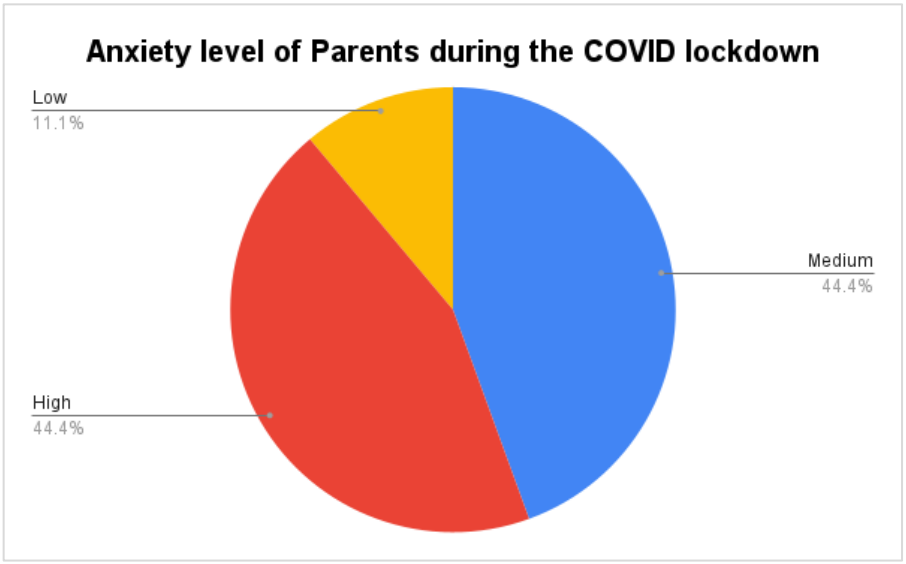

Fig-2 Represents the anxiety level of Parents during the Pandemic

Initial Anxiety Due to COVID-19 Restrictions

All participants reported feelings of anxiety upon learning about the COVID-19-related restrictions that would prevent them from being with their newborns. This suggests that the uncertainty and challenges brought about by the pandemic had a universal impact on their emotional well-being.

Communication During Separation

Communication patterns during the period of separation varied among parents. Some reported regular communication with their child, while others admitted to not communicating at all. This variability highlights the diverse strategies parents employed to stay connected with their newborns during this challenging time, the neonatal unit of Akanksha Hospital including the doctors had regular video calls in

Management of Surrogate Mothers with COVID-19

During the COVID-19 pandemic, our hospital accommodated 54 surrogates. Despite stringent precautions in place to minimize the risk of infection, a few surrogates tested positive for COVID-19. Out of the 54 surrogate mothers residing in our hospital, 19 tested positive for COVID-19, while 35 tested negative. However, it's important to note that all the surrogates successfully recovered from the virus without experiencing any adverse effects. Importantly, none of the newborns under our care tested positive for COVID-19.

Surrogacy's impact on a child's developmental milestones

Data interpreted that majority of the child found with normal developmental achievement of milestone. Among 38 children, 19 children were born in year 2017,

11 children were born in year 2018, 07 children were born in year 2019 and 1 child was born in year 2020.

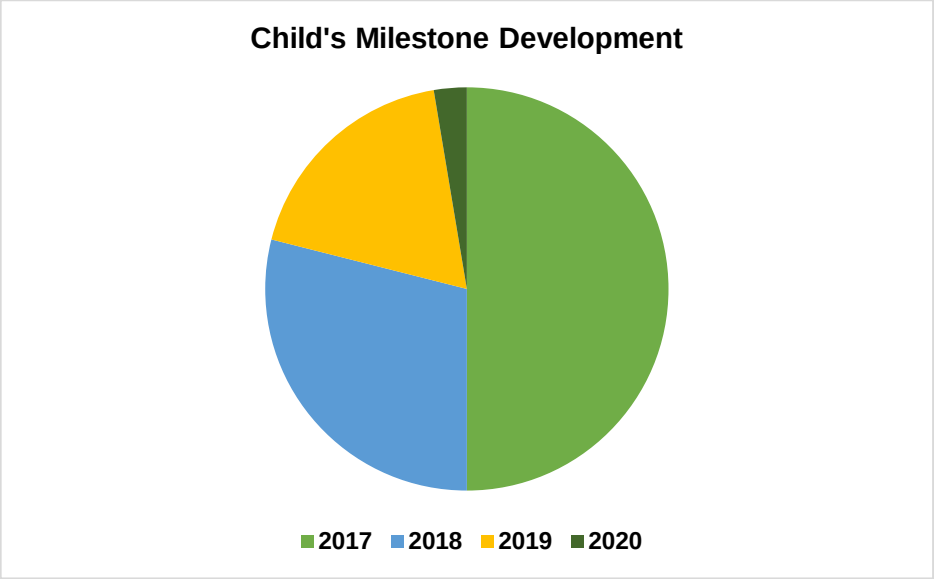

Fig-3 Represents the Development of child born through Surrogacy

Neonatal Outcome of Surrogacy

In our study involving 201 surrogate pregnancies, a total of 252 babies were born, consisting of 120 singleton births and 132 twin births, demonstrating variability in the outcomes of single and multiple births. The average birth weight for singleton babies was calculated at 2.161 kilograms, while twin babies exhibited a slightly lower average birth weight of 2.067 kilograms, indicating a discernible difference in birth weights between singleton and twin births. The analysis of the source of eggs used in the surrogacy process revealed that approximately 20.4% of the surrogate mothers contributed to the birth of children using intending parents' own eggs. The larger share, about 79.6% of births, was delivered from donor eggs. Women may seek the use of donor eggs for various reasons, encompassing factors such as poor egg quality, advanced maternal age leading to a decline in both the quality and quantity of eggs, conditions like Endometriosis or chocolate cyst, absent ovaries, and a history of repeated IVF failures. Furthermore, situations involving recurrent pregnancy loss or the absence of a uterus can also drive the necessity for utilizing donor eggs. Surrogacy is not typically considered as the initial option; it becomes a consideration after exhausting other possibilities, especially when a woman has attempted various options, and her age advances while the quality of her eggs declines. In such cases, surrogacy is pursued, providing an alternative for individuals facing these challenges and increasing the likelihood of a successful pregnancy.[1]

Discussion

The varying durations of separation and diverse emotions experienced by intending parents during surrogacy underscore the need for comprehensive support structures. The emotional impact of extended separations, differing child development outcomes, and universal anxiety highlight the importance of tailored coping strategies and enhanced support mechanisms. The results advocate for better policies, clinical guidelines, and improved emotional support within surrogacy procedures to aid intending parents during periods of enforced separation due to unforeseen circumstances.

The results indicate that despite comprehensive precautions implemented in the hospital, a few surrogates contracted COVID-19 during the pandemic. However, the positive outcome was that all affected surrogates effectively recovered without any apparent complications. It is notable that stringent measures in place might have contributed to the successful recovery and minimal impact on the surrogates' health. Equally significant was the absence of any newborns testing positive for COVID-19, affirming the efficacy of the hospital's preventative strategies in safeguarding the infants from the infection.

This success highlights the importance of robust healthcare protocols in controlling and managing infectious diseases, particularly in specialized settings like surrogacy hospitals. The outcomes of the study emphasize the critical role of preventive measures in minimizing risks and ensuring the safety of both surrogates and newborns.

It is critical to understand that the impact of surrogacy on milestone development is neither

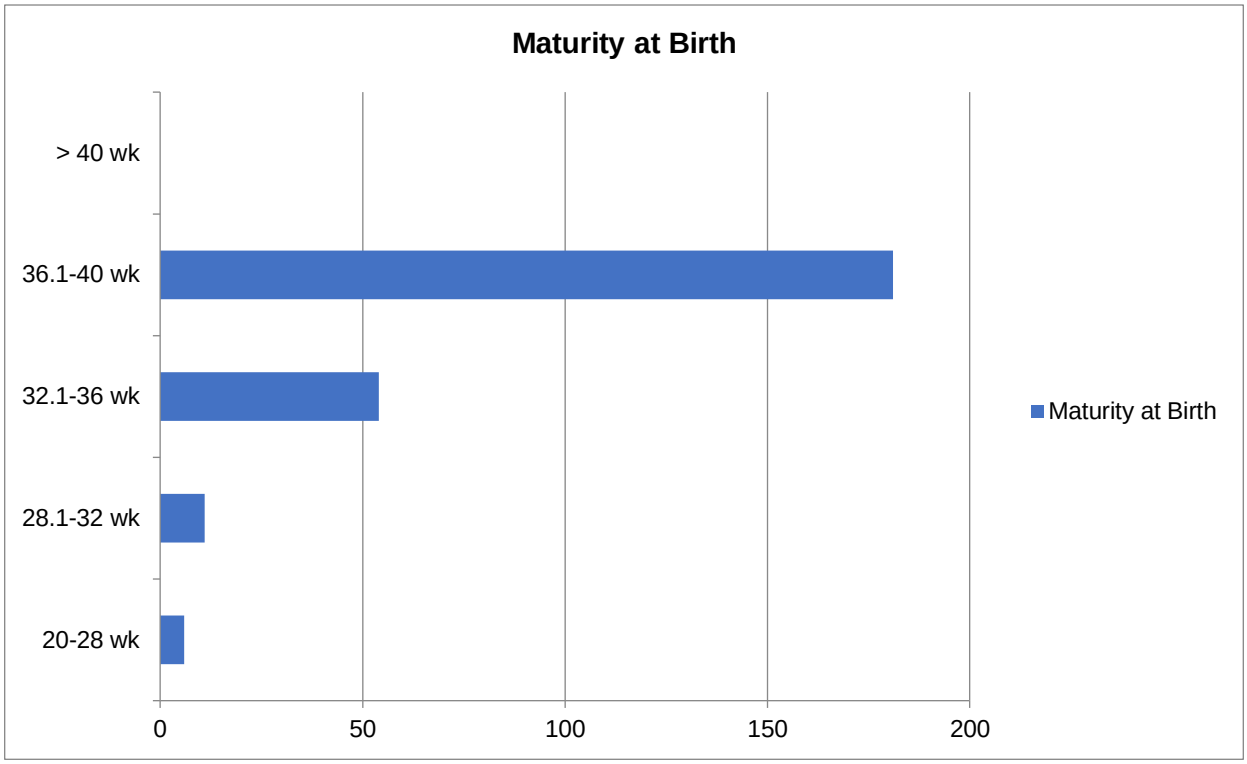

Fig 4- Indicates the weeks of maturity of the neonates at birth

detrimental nor favorable. It is determined by the family's attitude towards surrogacy, which includes open communication, emotional support, and the child's sense of belonging and acceptance within the family.

The most crucial part is that the child is reared in a loving, supporting, and communicative atmosphere in which their unique needs, questions, and concerns are recognized and handled as they develop and mature. Seeking expert advice and counselling can also be beneficial in supporting both parents and children as they negotiate the intricacies of surrogacy.

The analysis of 201 surrogate pregnancies revealed varying factors influencing birth outcomes. The study emphasized differences in maturity at birth, birth weight, and the source of eggs (self or donor). The majority of pregnancies derived from donor-egg sources, showing variations in average infant weight. The study highlights the need for further research to understand and enhance surrogate pregnancy management for optimal maternal and infant health outcomes.

This study is unique in its vast experience of the various aspects of surrogacy. In house surrogate dormitory gives us a lot of information about otherwise un explored aspects of surrogacy.

As a hospital, we provide continued care to the surrogate and her family members, there by leading to community building and empowering women around us.

A chapter authored by our team titled 'Exploring Social, Economic, and Emotional Aspects of Surrogacy Practice: A Retrospective Analysis of 106 Surrogate Mothers in Anand was featured in Red Biotechnology. Focusing on a study conducted at a single center in Anand involving 106 surrogate mothers, this chapter delves into the various facets of surrogacy in India. It emphasizes the importance of considering the surrogate mothers' perspectives, asserting their significance as essential participants in the surrogacy process. The study's results indicate the potential positive impact of compensated surrogacy on the lives of the surrogates. Financial compensation provided through surrogacy contributes positively to the social well-being of these women, supporting their children's education. It concludes by suggesting that appropriately administered surrogacy can offer benefits to both the surrogate mothers and intended couples, enabling the former to enhance their future prospects while assisting the latter in realizing their family dreams.[14]

Conclusions

The surrogacy procedure for needy couples is a boon, empowering surrogates and bringing beautiful

babies into this world. It creates happy families and connects families separated by miles, as there are no ethical, political, religious, or geographical barriers to it.

The study involving intending parents navigating surrogacy during the COVID-19 pandemic highlighted diverse experiences, including varying durations of separation and emotional complexities. Communication patterns differed, suggesting the need for tailored support mechanisms for intending parents in challenging circumstances.

Another study conducted during the pandemic revealed the successful recovery of surrogates who tested positive for COVID-19 and confirmed no virus transmission to newborns, indicating the efficacy of stringent hospital safety measures.

The studies emphasize the critical importance of providing a nurturing environment for children born through surrogacy, underlining the significance of addressing their unique needs and providing necessary support for both parents and children.

Furthermore, the retrospective analysis of 201 surrogate pregnancies showed significant variances in birth outcomes, particularly with donor-egg sources impacting infant weight. The study underscores the necessity for continuous research and strategies to optimize health outcomes for both surrogate mothers and infants, emphasizing the importance of enhanced prenatal care.

FUNDING

No external funding was received for the study.

CONFLICT OF INTEREST

This research paper does not report any conflicts of interest.

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Gestational surrogacy: 12-year experience of the first program developed in Argentina

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ABSTRACT

Objective:

To evaluate and share the experience of our Surrogacy program at Halitus Instituto Medico, which is the first one of its kind in Argentina. The study aimed to identify and describe demographic, physiological, social, and treatment-related factors associated with successful surrogacy outcomes.

Design:

Retrospective cohort study. Identification of all clinic consults for surrogacy was performed. Anonymized data on 1152 surrogacy consults occurring between 2011 and 2023 was extracted directly from the clinic database.

Results:

Between April 2011 and September 2023, there were 1152 consultations for uterine surrogacy, and out of these, 161 (14%) patients proceeded with the treatment. Eighty-four percent were couples while 21,7 % were single-parent projects. Main reasons for consultation were: male patients 346 (30.4%), obstetric factors 293 (30.4%) and uterine factors 254 (22.05%).

161 patients underwent 1 or more gestational surrogacy cycles. We achieved 127 (79%) pregnancies and 62 (48,8%) live births. The rate of multiple pregnancies was 3,1%.

Conclusion:

Gestational surrogacy is a global trend that sparks controversies and ethical debates. Despite this, it stands as a beneficial procedure, with a high success rate and a comparatively low risk of complications. The multidisciplinary collaboration of medical, psychological, and legal professionals is essential to carry out these treatments safely and effectively.

KEYWORDS: Gestational surrogacy, intended parents, gestational carrier, Argentina.

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MANUSCRIPT

Introduction

Gestational surrogacy (GS), also known as uterine surrogacy, is a well-known assisted human reproduction technique recognized by the World Health Organization (WHO). The process involves an individual or couple known as intended parents (IP) who receives assistance from a woman who lends her uterus to carry out the pregnancy (gestational carrier (GC)). This type of treatment is presented as an option for individuals who, for various medical, sexual, or gender reasons, are unable to fulfill their procreational desires. There are two main types of surrogacy: traditional and gestational. In traditional surrogacy, the surrogate mother's oocytes are used, making her a genetic parent along with the intended father. Gestational surrogacy, on the other hand, involves transferring an embryo from the intended parents or from donated gametes to the surrogate's uterus. In gestational surrogacy, the GC has no genetic connection to the child [(1)].

The first gestational surrogacy treatments date back to the late 1980s in the United States, and the first GC was identified as such in 1985 [(2)]. Since then, there has been a significant grow in the practice of gestational surrogacy in that country, with an increase of over 470% [(3)]. Worldwide, the demand for gestational surrogacy has been steadily expanding due to various reasons, including the complexity of adoption processes. According to a 2017 report from Cornell Law School (USA), only 14 countries worldwide allow gestational surrogacy. The report also notes that in 21 countries this practice takes place without economic compensation, and in 39 there is no regulation related to economic aspects. Regarding the prohibition of gestational surrogacy, the study mentions 50 countries that prohibit it and 72 that have not made any official stance on the matter [(4)].

According to the International Federation of Fertility Societies (IFFS) Surveillance 2016, doctors from 65 countries responded the following to the question, "Is gestational carrier arrangements permitted in your country?": Respondents from 24 countries (38%) noted that gestational carrier arrangements are allowed by statute or guidelines, respondents from 36 countries (56%) reported that it was not allowed, respondents from 8 countries were not able to answer the question and respondents from 8 countries that allow gestational carrier arrangements noted that traditional gestational carrier arrangements were not allowed [(5)].

In Argentina, there is currently no law regulating gestational surrogacy practices. According to Article 19 of the Argentine National Constitution, what is not prohibited is allowed, and this is the main reason why the first treatment was performed by Halitus. This legal loophole has led many patients to elevate claims to the corresponding legislative authorities in an attempt to draw attention to this deficit. Despite this lack of regulation, the scientific team at Halitus Instituto Medico in Buenos Aires began, over a decade ago, the creation of interdisciplinary teams to provide appropriate coverage and scope for this demand. We believe that care and follow-up should be equal for all parties involved, being able to support each one based on their individual needs. In this regard, the coordination of medical intervention with proper legal advice and ongoing psychological intervention throughout the process allowed for the first successful birth through gestational surrogacy in Argentina in 2011. Subsequently, legal precedent was established in 2013, marked by a magistrate's approval of the registration of the child born through this method directly under the names of her procreational parents [(6)].

The journey was long until 2017 when, thanks to a collective action by several LGBTQ+ families, a law was passed allowing babies born via GS in the city of Buenos Aires to be registered under the name of the procreational parents, provided that the following conditions are met before the treatment is performed: 1) they are minors born in the Autonomous City of Buenos Aires through the method of collaborative gestation; 2) the procreational intent of the parents has been expressed beforehand, freely, and informed; 3) the GC has unequivocally expressed a lack of procreational intent, and 4) the registration must be done preventively, with the GC data recorded in the file [(7)]. Currently, the registration process for newborns through gestational surrogacy in the Autonomous City of Buenos Aires is regulated by Directive 122/2020 of the “Dirección General del Registro del Estado Civil y Capacidad de las Personas” [(8)].

To ensure proper guidance and care for all parties involved, it is essential that a multidisciplinary team evaluate both the IP and the GC. This involves medical and psychological assessments, as well as legal advice, to carry out the treatment appropriately and safely. The creation of interdisciplinary teams for this purpose requires professionals not only proficient in their respective fields but also trained in this specific area. The presence of specialists in law, medicine, and psychology allows for the creation of recommendations to advance and sustain this practice in the absence of a regulatory legal framework. While gestational surrogacy in Argentina lacks a specific law, it is governed by multiple professional regulations that make it a feasible and secure practice.

The main objective of this study was to evaluate and share the experience of our Surrogacy program at

Halitus Instituto Medico, which is the first one of its kind in Argentina. The study aimed to identify and describe demographic, physiological, social, and treatment-related factors associated with successful surrogacy outcomes.

Materials and Methods

This is a retrospective cohort study to assess the 12-year experience of a Surrogacy Program at Halitus Instituto Médico.

Data collection and extraction

A retrospective identification of all clinic consults for surrogacy was performed. Anonymized data on 1152 surrogacy consults occurring between 2011 and 2023 was extracted directly from the clinic database. Data abstractor had experience in the field of uterine subrogation. All protected health information (PHI) was excluded from the data extraction. Inclusion criteria: All consults for uterine subrogation at Halitus Instituto Médico occurring between 2011 y 2023. Exclusion criteria: Cases with any missing data on main variables as described above. Determination of main variables to be extracted and definition of categories for each variable was determined by a panel of experts on the field. Main variables extracted included: age of intended parents, sex and gender, type of partner, diagnosis, type of treatment and pregnancy outcome.

The intended parents are responsible for the recruitment of surrogate mothers. The clinic is not involved in this process but is responsible for the medical and psychological evaluation and legal advice. All surrogate mothers must be of legal age (+18 years old), and preferably between the ages of 21 and 45 years. Certain situations may dictate the use of a carrier older than 45 years, but all parties involved must be informed about the potential risks of pregnancy with advancing maternal age. The carrier should have had at least one, term, uncomplicated pregnancy before being considered as a GC for the IP. She should not have had more than a total of 5 previous deliveries and no more than 3 deliveries via cesarean section and must have a stable family environment with adequate support to help her cope with the added stress of pregnancy [(9)]. They should not have any contraindications for pregnancy and should have a low obstetric risk.

During the psychological assessment of potential surrogate candidates, their motivations and treatment expectations are carefully evaluated. Family and group support are provided, if necessary, especially in addressing the repercussions of their decision. Fantasies, fears, and concerns are clarified, evaluating the resources and attitudes of each gestational carrier (GC). The detection of any ongoing psychological disorders is crucial. The previous maternal experience during pregnancy, childbirth, and the postpartum period is also considered.

Independent legal advice is mandatory for both procreational parents and gestational carriers. The legal team is experienced on how to register newborns in Argentina, and about the laws of the country where the parents and the baby will reside if they are foreigners. This point is crucial, as each country has very different legislation regarding children born in other countries whose parents decide to return to their country of origin.

The surrogate mother's endometrial preparation involves oral administration of valerato de estradiol 4 mg twice a day (Ronfase®) until achieving a minimum endometrial thickness of 7 mm and maintaining blood progesterone levels less than 1 ng/ml. Once these conditions are met, vaginal micronized progesterone is initiated at a dose of 400 mg twice a day (Utrogestán®). Since 2021, blood progesterone levels are measured the day before embryo thaw. If the progesterone levels fall between 7 and 10 ng/mL, subcutaneous progesterone at a dose of 25 mg/day (Aleterpure®) is added to the endometrial preparation. If levels are below 7 ng/mL, the embryo thaw is canceled and rescheduled. Embryo transfer takes place after 5 complete days or 132 hours after the start of progesterone.

The formation of embryos was carried out using either the intended parents' own gametes or donated gametes. For ovarian stimulation of the intended mother, antagonist protocols were utilized, along with recombinant follicle-stimulating hormone (rec-FSH) and either urinary-derived menopausal gonadotropin (UP-hMG) or recombinant luteinizing hormone (rec-LH) based on ovarian stimulation protocols. Final oocyte maturation was induced with either recombinant human chorionic gonadotropin (rec-hCG) or GnRH analogs, depending on the ovarian follicle count on the day of trigger. All fertilizations were performed using intracytoplasmic sperm injection (ICSI). Most cycles involved cryopreservation for future embryo thaw transfer cycles, but in some cases, fresh embryo transfers were performed. This segmentation of cycles was done for synchronizing the gestational carrier or for cases involving preimplantation genetic testing for aneuploidy (PGT-A). In the case of a fresh embryo transfer, the cycle synchronization between the intended mother and GC was achieved using contraceptive pills.

Some patients brought their embryos previously cryopreserved in other centers (either in Argentina or other countries), to Halitus. All patients were offered genetic studies for preimplantation genetic testing for aneuploidy (PGTA) and panels for monogenic

diseases, but not all chose to undergo these tests. Not all transferred embryos underwent PGTA test.

The study was approved by Halitus ethics committee and waiver of consent was granted by the ethics committee as all data included in the analysis was anonymized.

who consulted was 41.7 years, with the oldest being 70 years and the youngest 18 years old.

The rise in consultations throughout the years is remarkable, even in the face of a global pandemic (**Figure 1**).

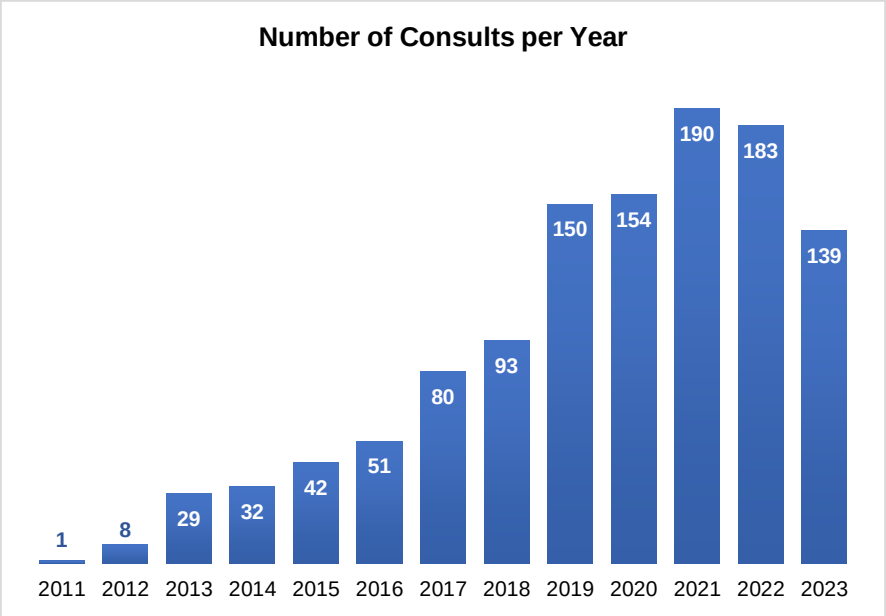

Figure 1. Number of consults per year from 2011 until 2023.

Statistical Analysis

A convenience sampling method was used. All participants with missing data were excluded from the analysis. Categorical variables are expressed as frequencies and percentage of occurrence. Continuous variables are expressed as means [95% confidence intervals (CI)] or median [interquartile range (IQR)] depending on distribution. Independent samples t-test or Mann-Whitney test were used to assess continuous variables based on the data's distribution, while categorical variables were compared using the chi-squared test or Fisher's exact test, where appropriate. Logistic regression models, Odds Ratios (95%CI) and Fisher exact test were computed to identify associations of different factors to successful surrogacy outcomes. All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC USA), with the risk of Type I error set at α=0.05.

Results

Over a period of 12.5 years (from April 2011 to September 2023), 1152 consultations were held by individuals expressing the desire for uterine surrogacy. Among these, 161 patients (14%) decided to proceed with the treatment. The average age of the patients

Among the interested patients, 745 (64.67%) were heterosexual couples, 225 (19.53%) were same-sex couples, and 182 (15.8%) were single-parent projects, of which 121 (10.5%) were men and 61 (5.3%) were women (**Table 1**).

The reasons for consultations from patients interested in this practice were: male patients 346 (30.4%), obstetric factors 293 (30.4%), uterine factors 254 (22.05%), recurrent implantation failure 110 (9.55%), unclear indication 71 (6.16%), advanced age 70 (6.08%), endometriosis 7 (0.61%), and transgender female 1 (0.09%) (Table 1). More detailed diagnoses are shown in **Table 2**.

Finally, 161 cases of uterine surrogacy were carried out. 51% of the treatments were performed by heterosexual couples, 30% by male same-sex couples, 13% by single men, and 6% by single women (**Table 3**). The average age of the procreational parents was 40.26 years. The diagnostic indications for uterine surrogacy are shown in Table 3.

There were 133 treatments with oocyte donation and 28 with own eggs (**Figure 2**). When the treatment involved own eggs, 20 cycles were deferred and 8 were fresh. In the case of egg donation, there were 97 deferred cycles and 36 fresh cycles (**Figure 3**).

	# Consults* (1152)
Age	41.69 (41.28-42.10)
Type of Couple	
Heterosexual couples	739 (64)
Same-sex Male couples	225 (20)
Single Male	127 (11)
Single Female	61 (5)
Diagnosis	
Male Patients	346 (30)
Obstetric Factor	293 (25)
Uterine Factor	254 (22)
Recurrent Implantation Failure	110 (10)
Without clear indication	71 (6)
Advanced Age	70 (6)
Endometriosis	7 (0.9)
Trans Female	1 (0.1)
NO	991 (86)
YES	161 (14)

** Data presented as mean (95% CI) or n (%)*

Table 1. Characteristics of all consults between 2011 and 2023.

Pregnancy rate with donated oocytes was significantly higher when compared with own eggs (**Table 4 & Figure 4**). Subgroup analysis revealed that the pregnancy rate with own eggs in fresh cycles was 63%, and when previously cryopreserved embryos were transferred (FET), the pregnancy rate was 55%. When donated oocytes were used in fresh cycles, the pregnancy rate was 89%, and with previously cryopreserved embryos, it was 81% (**Table 4 & Figure 5**). Pregnancy rates were significantly higher in donated oocytes, irrespective of the type of embryo transfer technique utilized (OR=5.19, p=00009) (Table 4). On logistic regression analysis, the only factor influencing successful pregnancy was the type of eggs used (donates vs own). Other factors including age, type of couple and diagnoses did not show any significant association with successful pregnancy.

We reviewed pregnancy outcomes on the 127 pregnancies that were achieved. Twenty-six pregnancies were ongoing (surpassed 20 weeks) at the time of this publication, 33 pregnancies resulted in miscarriage (26%), with 3 ectopic pregnancies, 62 pregnancies resulted in a live birth. So far, there have been 62 confirmed deliveries with a total of 64 children born (5 gestational carriers had elective double transfers). There were 3 fetal deaths (2 due to premature rupture of membranes at weeks 21 and 22, respectively) and 1 at week 36 with no diagnosis (**Table 5**).

No conflicts were reported between the gestational carriers and the intended parents, and all babies are registered in the names of the procreational parents.

	N	%
Male Patients		
Same sex couple	225	65.02
Single Male	121	34.98
Obstetric Factor		
Pregnancy contraindication	202	68.94
Recurrent Abortion	65	22.18
ICC	18	6.14
Thrombophilia	8	2.73
Uterine Factor		
Hysterectomy	182	71,75
Utierine malformation	30	11,81
Miomatosis	19	7,48
Uterine synechiae	10	3,93
Endometrial cancer	5	1,96
Cervical cancer	4	1,57
Thin endometrium	3	1,18
Arteriovenous malformation	1	0,39
No indication		
No desire to get pregnant	65	91,54
Fear of pregnancy	6	8,45

Table 2. Detailed Diagnoses of the initial consults.

	All Participants (n=161)	+Pregnancy (n=127)	-Pregnancy (n=34)
Age	40. 26 (39.32-41.20)	40.03 (38.95-41.12)	41.12 (39.06-43.17)
Type of Couple			
Heterosexual couples	82 (51)	59 (46)	23 (68)
Same-sex Male couple	48 (30)	43 (34)	5 (14)
Single Male	21 (13)	18 (14)	3 (9)
Single Female	10 (6)	7 (6)	3 (9)
Diagnosis			
Male Patients	67 (42)	59 (46)	8 (24)
Obstetric Factor	37 (23)	29 (23)	8 (24)
Uterine Factor	33 (20)	22 (17)	11 (32)
Recurrent Implantation Failure	16 (10)	9 (7)	7 (21)
Advanced Age	7 (4)	7 (6)	0 (0)
Endometriosis	1 (1)	1 (1)	0 (0)
Oocyte source			
OD	133 (83)	**111 (87)**	**22 (65)**
Own	28 (17)	**16 (13)**	**12 (35)**
Type of Treatment/Embrio Transfer (ET)			
Crio OD	97 (60)	79 (62)	18 (53)
Fresh OD	36 (22)	32 (25)	4 (12)
Crio OWN	20 (12)	11 (9)	9 (26)
Fresh OWN	8 (5)	5 (4)	3 (9)

Table 3. Characteristics of the population that completed treatment.

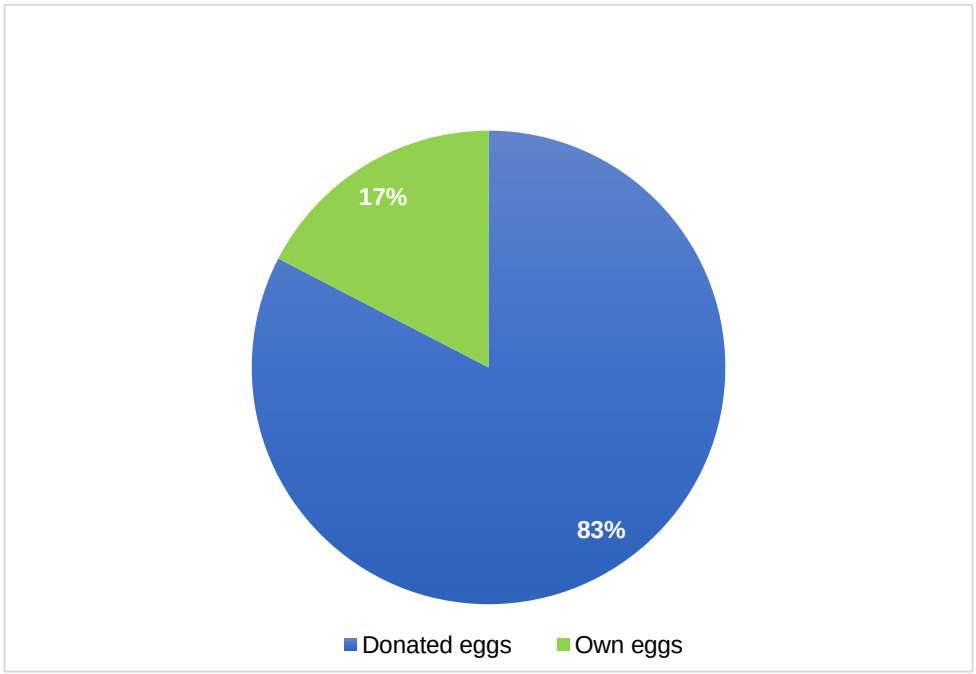

Figure 2. Oocyte origin.

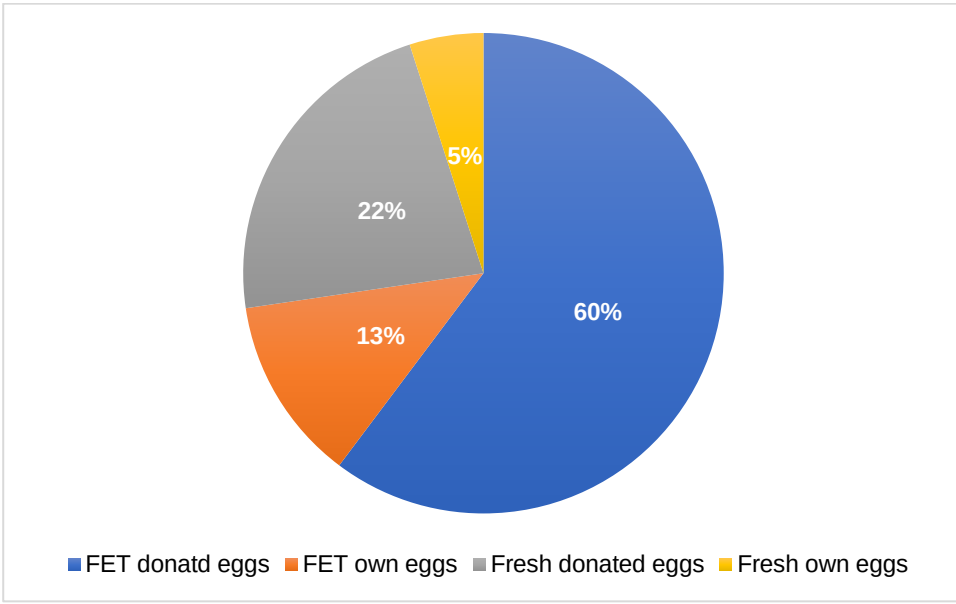

Figure 3. Treatment – Embryo transfer (ET) type.

	+ Pregnancy (n=127)	- Pregnancy (n=34)	OR (95%CI)*	p-value*
Oocyte source				
OD (n=133)	111 (83)	22 (17)	**5.19 (1.98-13.96)**	**0.0009**
OWN (n=28)	16 (57)	12 (43)		
Type of Treatment/Embrio Transfer (ET)				
Crio OD (n=97)	79 (81)	18 (19)	**4.78 (1.61-14.51)**	**0.0051**
Crio OWN (n=20)	11 (55)	9 (45)		
Fresh OD (n=36)	32 (89)	4 (11)	**7.28 (1.08-49.46)**	**0.0412**
Fresh OWN (n=8)	5 (63)	3 (37)		

*Data shown as n(%) *Logistic regression model and Odds Ratio (OR) calculations.*

Table 4. Factors associated with successful pregnancy.

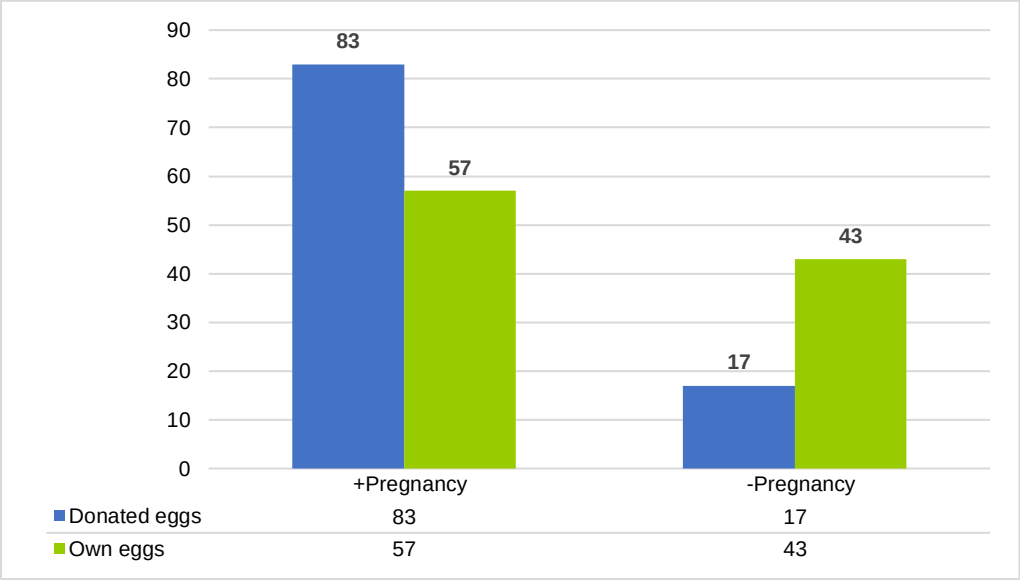

Figure 4. Oocyte source in successful pregnancy vs unsuccessful pregnancy.

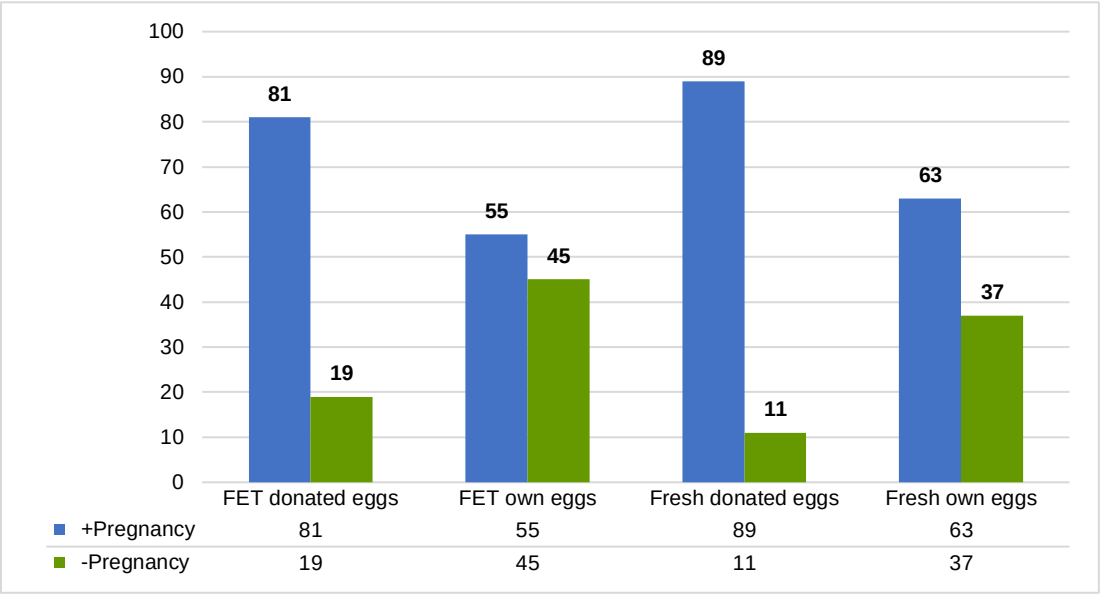

Figure 5. Type of ET in successful pregnancy vs unsuccessful pregnancy.

	N	%
BIOCHEMICAL ABORTION	8	6
MISCARRIAGE	25	20
ECTOPIC PREGNANCY	3	2
ONGOING PREGNANCY	26	20
FETAL DEATHS	3	2
LIVE BIRTH	62	49
Total	**127**	**100**

Table 5. Pregnancy Outcomes.

Discussion

Argentina has become an attractive option for gestational surrogacy, for both local and foreign patients, due to its openness to new family structures without discrimination based on gender, sex, origin, or ethnicity. In a global context where many countries restrict possibilities for foreign patients, Argentina provides legal and medical security for these treatments.

The multidisciplinary team has proven to be essential in approaching and monitoring these patients. The collaborative efforts of a team established from the outset, all within the same institution in continuous communication, guarantee that Halitus' program delivers personalized treatment to each patient. This approach involves professionals—doctors, nurses, embryologists, psychologists, and lawyers—coming together, sharing insights and experiences to provide the best for our patients.

Although there has been a constant increase in consultations over the years, only a small percentage of patients seeking advice can finally undergo treatment, possibly due to economic, ethical, or social factors. Our retrospective review did not allow for the identification of these factors.

Contrary to popular belief, surrogacy is not exclusive or mostly requested by same-sex couples or single men. In fact, data shows that heterosexual couples, especially those with medical issues related to uterine dysfunctions, are the ones who most often turn to these techniques. However, as shown in our analysis, a higher percentage of male individuals seeking consultation undergo the treatment, compared to heterosexual couples or single women (20 vs 11%).

As described, pregnancy rates with egg donation are higher than those with own eggs. Despite this, pregnancy rates with own eggs were very acceptable in this cohort (57%).

Another consideration to take into account is the risk of multiple pregnancies. In the United States, the transfer of two or more embryos is done in almost 80% of cycles with surrogates, and less than 20% opt for elective single embryo transfer [(10)]. Although transferring more than one embryo is discouraged due to the risk of multiple pregnancies, there are special considerations that support it. In our intervention model, this and other specificities are addressed both medically and psychologically. In these consultations surrogates and intended parents, with proper guidance, can make decisions regarding the number of embryos to transfer. In our cohort from the 161 treatments, 5 (3.1%) resulted in twin pregnancies that led to 9 live births (one baby died postpartum due to complications from prematurity).

CONCLUSIONS

Gestational surrogacy is a global trend that sparks controversies and ethical debates. Despite this, it stands as a beneficial procedure, with a high success rate and a comparatively low risk of complications.

Considering the possibility of human life gestating outside the maternal womb, involving the participation of others, gives rise to arguments both in favor and against. While some question the ethics of exposing gestational carriers to the risks of being pregnant with no procreational desire of their own, other voices defend a woman's right to choose what to do with her own body.

Arguments in favor of LGBTQ+ rights and the capacity of mentally competent adults to collaborate in creating life also align with this perspective.

It is crucial to establish relevant regulations to protect all involved parties, especially unborn children. Beyond the controversy, it is undeniable that gestational surrogacy is a concrete solution that brings hope to those who have lost gestational capacity or harbor the desire for a child.

In the professional field dedicated to this practice for decades, efforts persist to establish the legitimacy of gestational surrogacy within an interdisciplinary team working collaboratively within the same institution. This involves integrating medical, psychological, and legal expertise, prioritizing ethics, respect for human beings, and adherence to the law as regulatory frameworks. The findings from this study, reflecting the experience of our center, indicate that this can be achieved with high rates of success, when performed by a multidisciplinary and experienced team.

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CONFLICT OF INTEREST

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Embryological Perspectives on Gamete and Embryo Donation

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ABSTRACT

This article addresses the issue of gamete and embryo donation from the perspective of the assisted reproduction laboratory, where the so-called "clinical" embryologists work making all the current variants of in vitro fertilization including the andrology laboratory, oocyte collection, conventional insemination or through ICSI, embryo culture, gamete and embryo quality evaluation, embryo transfer, cryopreservation of gametes and embryos, preimplantation genetic studies, results analyses and quality control, assessment and improvement. To think that the responsibility of an ART laboratory only attains the strictly technical or logistical areas is an error or a simplification that excludes embryologists from other important matters. Clinical embryologists have the obligation to ensure that procedures follow strict ethical rules, highlight deviations or errors from these canons, and refuse to act in cases of violation of said standards. Donating embryos to assist in others´ efforts on building a family is an important option for patients who are considering the disposal of cryopreserved embryos, in excess those needed to meet their own fertility goals.

Gamete donation, a more widespread procedure, can help us to better understand certain aspects of embryo donation. Donation must be a free transaction, not influenced by guilt or any other type of pressure or coercion of any kind.

We are facing a totally new issue because we are the only species on the planet that can manipulate our own gametes and embryos in a context where assisted reproduction represents a dramatic challenge to the social values that govern our way of being born, without precedent in human history.

KEYWORDS: Fertility, Embryology, Laboratory, Bioethics.

MANUSCRIPT

The International Glossary on Fertility and Infertility Medical Care, agreed upon by the main fertility societies in the world and published in each of their scientific journals in 2017 [28], establishes that the embryo donation for reproductive purposes is an assisted reproduction treatment (ART) cycle that consists of the transfer of an embryo resulting from the union of gametes that did not originate from or are not

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specific to the woman who receives that embryo or her male partner, if any.

The definition seems obvious but the clarification "if any" places it in another arena: it refers to the new infertility definition also provided by this consensus: "a disease characterized by the impossibility of achieving a clinical pregnancy after 12 months of regular sexual intercourse and without protection or by a person´s inability to reproduce, either as an individual or with his or her partner. Infertility is a disease that produces an inability due to an impediment of the reproductive function".

It is then clear that the "recipients" of an embryo-donation can be the partners made up of a woman and a man, two women, two men or a woman or a man. Assisted reproduction with third party intervention (that is, people other than those who wish to reproduce) has made it possible for infertile people to have more options when it comes to starting a family. That is medicine: in the face of the wonderful but severe nature (Darwin called it the nature of bloody teeth and claws) we oppose vaccines to diseases, crops to hunger and, in our case, assisted reproduction to infertility and forms of reproduction that do not follow the traditional canon of a man, a woman and two children (one of each sex, if possible…).

This modern definition coincides with the Pronouncement of the Inter-American Commission on Human Rights regarding the "Costa Rica Case", a country that prohibited assisted reproduction techniques (Artavia Murillo et al. Case - In Vitro Fertilization - Vs. Costa Rica, http:// www.corteidh.or.cr/cf/Jurisprudencia2/ficha_tecnica.cfm?nId_Ficha=235):

- Infertility is a disease. The prohibition of assisted reproduction is discrimination.
- Reproductive rights are human rights.
- The embryo is not subject to the right to life as people are. Access to rights is a gradual process and is not established immediately after fertilization.
- The woman is the right holder, not the embryo.

This article addresses the issue of gamete and embryo donation from the perspective of the assisted reproduction laboratory, where the so-called "clinical" embryologists work making all the current variants of in vitro fertilization including the andrology laboratory, oocyte collection, conventional insemination or through ICSI, embryo culture, gamete and embryo quality evaluation, embryo transfer, cryopreservation of gametes and embryos, preimplantation genetic studies, results analyses and quality control, assessment and improvement. To think that the responsibility of an ART laboratory only attains the strictly technical or logistical areas is an error or a simplification that excludes embryologists from other important matters. Clinical embryologists have the obligation to ensure that procedures follow strict ethical rules, highlight deviations or errors from these canons, and refuse to act in cases of violation of said standards.

Donating embryos to assist in others´ efforts on building a family is an important option for patients who are considering the disposal of cryopreserved embryos, in excess those needed to meet their own fertility goals. Another way to receive donated embryos is through their in vitro origin after the double donation of oocytes and sperm, a procedure that raises ethical questionings different from those stated herein [19]. The embryo donation cannot be equated to the adoption of minors because the embryos are not simply minors. It is important to use the appropriate terminology to refer to this procedure. The use of the term "adoption" for embryos is inaccurate, misleading, and could place an inappropriate burden on infertile recipients. Since adoption refers to a specific legal procedure that establishes or transfers the parentage of existing children, the term donation should be used for embryos [9]. The adoption of girls and boys is another important option available to help women and men who want to start their families, also providing loving homes for those in need [9].

Neither a zygote (a fertilized oocyte that shows two pronuclei) nor an embryo are "minors" [15,13, 12] mainly because:

- They have individual cells that are too independent to constitute an individual.
- They lack a structured constitution.
- They are a cluster of cells (embryonic tissue) that can potentially develop into a new individual, or into more than one individual, as in the case of a set of twins. [27] demonstrated this potential by dividing 4-cell embryos into 4 parts on day 2 (placing 1 cell in each of the 4 receiving zonas pellucidas, emptied of their original cells), originating 4 blastocysts at the sixth development day.
- They can generate a tumor, a hydatidiform mole or a chorioepithelioma, and not a person.
- An embryo generally carries several genetic abnormalities that cause many embryos to fail implantation or, if they do so, to be lost very early in their development.
- Depending on maternal age, between 40 and 90% of “good quality” embryos have been reported as aneuploid [18]

However, embryos deserve a “special status” between simple cells and human beings, being an entity that can potentially develop into a person [6]. Moral philosophers have argued about the moral status of the human early embryo as a “special entity, an intermediate stage between an object and a person, which deserves respect and protection but which can be used for research, therapeutic purposes or be destroyed if it is not going to develop into a child” [5,11] . The human embryo deserves greater respect than other human tissues because of its potential to become a person and its symbolic value to many people. However, it cannot be treated as a person because it still has not developed its characteristics as an individual, it still has not established itself as an individual, and may never develop its biological potential [7] We are holders of a deep moral intuition that tells us that human embryos are not just things, they are something more than the sum of sperm and oocytes or a simple accumulation of cells, and they shall not be treated as products or commodities (raw materials). Clinical embryologists must know that in ethics language is never neutral: there is a big difference between the fact of feeling owners of a life and the fact of having been entrusted a life in custody (which will potentially develop, or not, into a person) [21]. The use of embryos for therapeutic purposes is not the same as their use as if they were raw materials [1].

Compensation

The sale of embryos is then ethically unacceptable, and donors shall not be compensated for their donated embryos. However, it is legal for the clinic to charge a professional fee to potential recipients for embryo thawing, embryo transfer procedure, and screening of infectious diseases on both recipients and donors. Physicians and employees of an infertility clinic shall be excluded from participating in embryo donation (as donors or recipients) within said clinic.

Gamete donation, a more widespread procedure, can help us to better understand certain aspects of embryo donation. In procedures that involve egg or sperm donation, it is customary to financially compensate the donors ("loss of earnings compensation" for absences or "travel expenses"). This expense compensation often poses an ethical dilemma since, although the service offered by fertility clinics is far from being an event where rich women buy eggs from poor women, it is also far from being a mere compensation of expenses, since what to some people may be a "per diem" for expenses, to others it is certainly a salary. Participants in a symposium on ethical and legal aspects that took place in Buenos Aires in 2011 [2] were asked if they thought that it was a donation or a sale, since all the people who give their gametes to be used in the extraction of embryos receive financial compensation. About a third of those surveyed answered that it was a donation, a third said it was a sale, and the remaining third said they did not know or did not want to answer. When asked if they should be financially compensated in a different way according to the donor's phenotype (that is, if it is not clear, that those with certain more socially "valued" phenotypes should be paid more), an 85% answered no but a 15% said they didn't know. No one said yes, although some later commented that they usually did it that way at their workplaces.

In fact, an advertisement for an oocyte bank announces that its donors are "physically perfect and mentally healthy, without bad habits or vices" and that "they have a strong desire to share the happiness of being a mother with other women", since most of them are mothers "of at least one healthy child”. Furthermore, the same clinic offers "VIP" egg donors, possessing "extraordinary beauty and high educational level".

Thus, it is essential to be clear that:

- Both gamete and embryo donation must not be for profit or commercial purposes.
- Compensation must be intended to repair the physical discomfort and travel and labor expenses that arise from the donation; In no case can it be an economic incentive for the donor.
- Any advertising campaign or other activities, aimed at promoting the donation of tissues, gametes or embryos by authorized specialized centers, must respect the altruistic donation nature, and may not, in any case, encourage donation by offering financial benefits.
- The financial remuneration that exceeds the mere compensation for the donation of tissues, gametes and embryos, as well as the promotion or advertising that encourages the donation of cells, tissues and gametes by specialized health centers, authorized by offering compensation or economic benefits contrary to the provisions of law, shall be considered serious offences.

While The Practice Committees of the American Society for Reproductive Medicine (ASRM) and the Society for Assisted reproductive Technology (SART) advised in one of its most important guidelines (2008, then replaced by a new document in 2013) that vitrification was still an experimental technique, the proliferation of oocyte banks in the United States, the advertisements for apollonian men in sperm banks or "VIP" women in reproductive egg donation programs, or the cover stories in certain popular magazines where the interviewees answered as if they were providing cryopreserved oocytes for donation comparable to selling frozen asparagus or sardines, were clear

examples of the misuse of things that cannot be sold, such as blood or transplant organs.

The concept *res extra commercium* derived from Latin ("something outside of commerce") is a doctrine originated in the Roman law that states that certain things may not be the subject of private rights and therefore, they can neither be sold or purchased [20] The donation must be a free transaction, not influenced by guilt or any other type of pressure or coercion of any kind. The use we give to language will play an important role in this decision-making.

Language

The first term that should be of concern to us is the one that we ourselves, embryologists and reproductive health doctors, have used in some occasions to refer to the biological structure that we are donating, and that we precisely did not know how to define. “Pre-embryo” was used along with “concept” (only in the United States) or “early embryo” to define the stage of development that occurs between the end of fertilization (zygote) and the emergence of the primitive embryonic line, from the 12th to the 14th day of life. From day 12-14 onwards, biological individualization is guaranteed, and we could then call it “embryo”, and from the third month of gestation until birth, “fetus” [14,11]. While for some authors this term has been invented by some of them to avoid moral accusations or pressure from the tabloid press, for others "pre-embryo" is a “fabricated” term that no embryologist has approved and that no textbook uses [24].

Some national dignitaries that are critics of techniques that involve "human life" are epitomes of the Manichaean use of the language and do not blush when instituting "the day of the unborn child" or when attacking research work with stem cells derived from donated embryos (a technique that uses embryonic tissue in order to study how to improve the lives of millions of people suffering from incurable diseases), at the same time that carry out fraudulents *casus belli* (that is, an act or event that causes a war or is used to justify it) that brings about the loss of countless human lives, including many civilians, ignoring international humanitarian laws and international conventions, cutting off funds for critical social plans, while proclaiming to defend “a culture of life where the strong protects the weak and where we recognize the image of our Creator in every human life” [1].

"Donation" is a gift without payment involved (a definition that is obvious) or, more specifically, the "liberality of someone who freely transmits something that belongs to him in favor of another person who accepts it". From Ethics, "Egg donation" then seems correct [3].

Another way to use language erroneously is through its "domestication". This is how a fertility clinic advertises its services on the local subway with drawings of a blue female bird, wearing a pearl necklace, a purse and outstanding eyelashes, and a kind of male bee (a drone) carrying an office briefcase. The drawings represent the following idea: "when the little bird and the bumblebee can't have babies, turn to our clinic". We could think of a certain tendency to "infantilize" language, rather than domesticate it, but it happens that even a child knows that bees and birds do not procreate, and that, because of this, they are infertile among themselves. We should perhaps be less severe in our assessment and alternatively think that the clinic or those responsible for the propaganda have wanted to soften and provide a dose of humor to a topic that is thorny or painful for patients.

Other advertisements from some clinics that offer egg donation services seem to use language that is somehow between altruistic and childish. An advertisement says that donating oocytes is “a very small gift” (it doesn't even say “small”), treating the donors as if they were girls who do not understand what the matter is about. Others say: "giving is the best way to receive; donate eggs"; "everything that is not given is lost; your eggs too... we will compensate your generosity"; "it pays me to donate eggs" and "it pays me to donate semen". What is it that you are going to receive, according to the advertisement? The thanks, the inner satisfaction for the altruistic duty fulfilled or simply money? "You are young and you have thousands of them... become an egg donor". She also has a lot of hair and could donate it to a wig factory. Surely, since you are young, you also have thousands of minutes left over, and you could donate them to another charitable activity. It is essential to notice the difference between donating eggs and donating hair, time, or money.

The way we handle certain altruism in our society has been masterfully revealed by biologist Robert Trivers, when he writes: “The proof that self-deception acts in the service of deception is the denial of deception, the unconscious management of selfish and deceptive tricks, the establishment of a public image that looks as if it was altruistic and as a beneficial and useful person to other people´s life” [26].

On some occasions, the term “recruiters” has been used as slang to refer to those women, generally former donors, who in turn look for new donors. This unfortunately coincides with the negative opinion of certain general public and some members of the medical profession who see all this as something negative [16]. This extreme distortion of the language in the form of jargon can be harmful and the only thing it achieves is that the donors´ efforts are not rewarded, that their genuine interest in helping is not recognized

(although at the same time they feel that it is correct or necessary to be economically compensated), nor the good intention and performance of many professionals involved and that, in the end, those people who need to complete a family are harmed.

Embryo donation is not exactly the same, nor has it been handled by clinics or advertising in the same way, as gamete donation. The donation of oocytes or sperm is an individual act, in theory, independent. The decision to donate eggs or sperm could be influenced by the opinion of the donor's partner. However, the decision to destroy or cease the egg or semen cryopreservation is the exclusive responsibility of the person who originated those cells, never of his or her partner or other family members. Likewise, the act of donating embryos already produced in vitro and cryopreserved does not involve the woman in the same way: while one is subject to ovarian stimulation and undergoes surgery, the other only must sign a consent or, at most, agree to certain additional studies. Despite these significant differences, it is illustrative and instructive to relate both types of donations because the experience accumulated with gametes can shed light on a less frequent practice which, in general, we have less experience with. Furthermore, in the same way that there are "VIP" oocyte donors, there could also be "VIP" embryo donors.

Consent

Patients who decide to donate their embryos to other people or couples must clearly know their motivations and understand without confusions the meaning of what they are going to do. All embryo donors must sign an informed consent document indicating their authorization to use their embryos for donation. Couples who may potentially be embryo donors should be informed about all aspects of their medical treatment and the psychological and ethical issues relevant and inherent to embryo donation. Embryo disposal options should be discussed with their doctor prior to cryopreservation. Current options include:

- the future use of embryos by the couple through cryopreservation,
- the donation of cryopreserved embryos to other infertile couples,
- the donation of embryos for research, including stem cell research,
- the cessation of cryopreservation, which means the destruction of the embryos.

All potential donor couples should be notified that additional testing may be necessary if they choose to donate their embryos and, if necessary, offered psychological counseling. After couples have completed their own reproductive attempts, embryo disposition options should be reevaluated.

Informed consent is also essential for embryo recipients, who must take full responsibility for the embryo and any child or children who may result from the transfer. Recipients must release both the embryo donors and the assisted reproduction clinic from any liability for any possible pregnancy complication or other unforeseeable embryo donation complications.

By no means can a general IVF consent include the "fine print" formula that states that, when patients do not specify their embryo donation, it is then automatically interpreted that they do donate them. On the contrary, there must be a specific consent where all the details are clearly stated but not in small print.

In special cases in which the couple has not specified what to do with the leftover embryos and contact with them has been lost, or they have left the decision of what to do with them in the hands of the ART clinic, said embryos are called "abandoned" embryos [10]. These situations pose an indefinite storage problem to the ART clinic, including the space and cost that this implies. For these particular cases, it is important that the consent clearly states that the ART clinic can dispose of those embryos if no patient has contacted the clinic for a specified period of time even though the clinic has attempted to contact them, without success [10].

Then, the issue of what to do with these "abandoned" embryos arises. A clinic can choose to continue cryogenic storage indefinitely or discard the embryos. Given the legal uncertainty of these embryo status, many clinics around the world choose the indefinite storage. By no means could embryos be donated to other couples or given for research [10], since no one has agreed upon said intention.

The right to be informed

The right to be informed about genetic origins, and in particular the right to know that one was born through assisted human reproduction with donor gametes or donated embryos, is unavoidable, since every person has the right to know that he or she was born through assisted human reproduction with gametes or embryos from a donor.

Likewise, although donations are anonymous to guarantee the privacy of both donors and recipients, the right to know must also be guaranteed, since every person, who has been born through assisted human reproduction techniques with gametes from a donor, is of age and mature enough to request from the specialized center involved, information related to the donor's medical data, when relevant to his or her health.

The use of genetic platforms or panels to genetically explore the donors´ genome is a more distant possibility because the donors´ will is needed to undergo such studies (in the case of oocyte or sperm donors it is different because for some centers this is essential and the donor would be listed among the mandatory studies) and because the interpretation of these results may lead to confusion and baseless fears, such as studies for late-onset diseases [17]. In other words, beyond the essential and mandatory studies required before a donation, the rest is an area still under discussion. We are all mutants and, if we search information, we will find out that we all have some predisposition to suffer from something, mild or severe, serious, or benign.

Conclusion

We are facing a totally new issue because we are the only species on the planet that can manipulate our own gametes and embryos in a complete *de novo* way.

We know that males of some fish species can imitate females (changing color and behaving as them) and release their sperm exactly at the moment when true females are spawning, mixed among themselves. The territorial male believes that two females have laid eggs for him, but in fact he has been deceived: the "cross-dressing" male has inseminated the eggs before he has [4,25].

Although some fish like the one in the example and other animals may have behaviors that in some way represent a form of gamete manipulation, technology has allowed humans to do it much better than fish [2]. Within only 50 years we have gone from a reproduction system where conception was largely unpredictable, sex was closely related to conception and there was a natural inheritance of genes, to another where (at least in societies with access to technology):

- There are effective contraception methods and female independence from non-planned pregnancy,
- There are alternatives to natural reproduction,
- The offspring sex could be open to selection,
- Gene therapies could modify natural gene inheritance.

We find ourselves, then, in a context where assisted reproduction represents a dramatic challenge to the social values that govern our way of being born, without precedent in human history.

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Motherhood in Female Same-Sex Couples: Reception of Oocytes from Partner (ROPA method): Review Article

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ABSTRACT

The evolving concept of "family" reflects contemporary social changes, influenced by historical and cultural shifts. This review explores unconventional family models, focusing on same-sex families, particularly female same-sex couples. As advancements in assisted reproductive techniques (ART) empower these couples, the Reception of Oocytes from Partner (ROPA) method gains popularity. ROPA involves active participation of both partners in conception, with one as the oocyte provider and the other as the gestational mother. This review delves into clinical, ethical, and psychosocial aspects of ROPA, comparing it with other ART options like donor intrauterine insemination (DIUI) or in vitro fertilization (IVF). A comprehensive bibliographic search conducted in 2023 forms the basis of this exploration. Historical perspectives on ART's acceptance for same-sex couples, legislative changes, and global variations in donor anonymity are discussed. The ROPA method's procedural details, including donor selection and the roles of the genetic and gestational mothers, are outlined. The review also emphasizes the impact of donor anonymity laws on decision-making. Roles and responsibilities in the ROPA method are explored, with a focus on the reciprocal and reverse ROPA approaches. Medical indications, potential benefits, and the impact on obstetric risks are scrutinized. The review concludes with insights into motherhood in female same-sex couples, highlighting the prevalence of children raised in such families across diverse regions in the United States. This comprehensive examination aims to provide practitioners and patients with valuable insights into the clinical, ethical, and psychosocial dimensions of the ROPA method, fostering a better understanding of its advantages in comparison to other ART options.

KEYWORDS: ROPA method in lesbian couples. Reception of oocytes from partner. In vitro fertilization with reception of oocytes from partner.

MANUSCRIPT

Introduction

Over the years, the concept of "family" has evolved; largely due to social changes, but also to the historical and cultural moment we are living. Family models in modern society or unconventional families range from those composed of single parents by choice (single-parent families), families with children from different partners, reconstituted families resulting from divorce or remarriage (reconstituted families) to families composed of same-sex couples (same-sex families)[(1,2)]. Same-sex families may consist of two men or two women. Similarly, the couple may live

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alone, with their own children, adopted children, or children conceived through assisted reproductive techniques (ART) or through alternative routes to procreation within the framework of a conventional couple[1]. Thanks to advances in ART, same-sex couples seeking to form a family have benefited, and as a result, social acceptance is increasing; with this, the concepts of paternity and maternity have been redefined[3].

Female same-sex couples face a biological necessity when seeking motherhood, which is the need to use donor sperm to achieve the formation of a zygote [3]. Because of this, nowadays female same-sex parent families can choose to undergo donor intrauterine insemination (DIUI) or pursuing ART such as in vitro fertilization (IVF)[3]. Although both partners have the potential to be birth mothers, in most cases, only one of the women desires to become pregnant by donating the oocytes and carrying the pregnancy. However, the non-genetic partner in the couple is limited in actively and biologically participating in the pregnancy[3].

Reception of Oocytes from Partner (ROPA) method consists of an ART for female couples in which both women take an active role in the conception of the newborn[3,4]. One partner is the oocyte provider (genetic mother) and the other receives the embryo and carries the pregnancy (gestational mother)[3,4]. These method is also called co-in vitro fertilization (Co-IVF), lesbian shared IVF, intrapartner oocyte donation, shared motherhood IVF[3].

Objetive

In recent years, ROPA treatment has become increasingly accepted among practitioners and patients. Since ROPA offers certain advantages over other ART for female couples, the aim of this work is to review the clinical, ethical, and psychosocial aspects of ROPA method that motivate more female couples to choose this ART versus DIUI or IVF.

Methods

A bibliographic search was conducted in July 2023 on electronic databases, Medline (PubMed) and Google Scholar that included information about the ROPA method in female same-sex couples. The first search included articles on new family models, homoparental families, assisted reproductive techniques in same-sex couples and subsequently, articles on the ROPA method in female same-sex couples.

The keywords used in the search were the following: "nuevos modelos familiares", "new family models", "homoparentality" "homoparental families", "ART in same-sex couples", "ART in lesbian couples", "ROPA method in lesbian couples", "ROPA method", "shared motherhood", "reciprocal ivf", "reciprocal in vitro fertilization", "assisted reproduction in lesbians", “ROPA method in lesbian couples”, “reception of oocytes from partner”, “in vitro fertilization with reception of oocytes from partner”. Publications in both English and Spanish were included, without a date limit. Neither was any type or design of publication excluded since the literature published so far on the subject is somewhat limited. In addition, the references of the selected articles were reviewed since articles with relevant information were included.

Results

Assisted Reproductive Techniques Throughout History

Some theories propose that the environment in which children of same-sex families are born may not be suitable for them, which is why for a long time, female couples were denied access to intrauterine insemination (IUI), donor sperm insemination (DSI), and other assisted reproductive techniques (ART)[5]. The first sperm bank in Spain was established in 1977 with the goal of studying and treating reproductive issues in both men and women, mainly to be able to give life [6]. In 1990, in the United Kingdom, thanks to the Human Fertilization and Embryology Act, female couples achieved greater reproductive equality with access to donor sperm insemination (DSI) and egg donation (ED)[2]. In Spain, in 2005, with the "Equal Marriage" Law (Ley 13/2005), the rights of homosexual couples were equalized with those of heterosexual couples[6]. In 2010, Australia and New Zealand implemented the Assisted Reproductive Treatment Act, which allowed single women and female couples to access fertility treatment and assisted reproduction[7]. In 2013, the American Society for Reproductive Medicine established that access to reproductive technologies should not be restricted based on sexual orientation or marital status[7]. In 2015, the U.S. Supreme Court also legalized same-sex marriage[7]. Thanks to these advancements, it's possible nowadays for both women in a same-sex couple to biologically participate in pregnancy: one providing the eggs (donor, egg donor, partner donor, or genetic mother) fertilized with donor sperm, and the other receiving the embryos and gestating them (recipient, gestational partner, or gestational mother)[8,9]. This method of reproduction is known as Reception of Oocytes from Partner (ROPA), in vitro fertilization (IVF) with Reception of Ova from Partner (ROPA), or co-IVF, and was first described in 2010 [6,8].

ROPA Method

The ROPA method consists of performing controlled ovarian stimulation and ovarian puncture on

the genetic mother; subsequently IVF with an anonymous or known donor in accordance with the legislation of the country where the procedure is carried out[10]. Once the eggs are fertilized, the embryos are left in culture[10]. The gestational mother undergoes a different hormonal treatment to prepare the uterine lining[10]. Once 3 to 5 days of embryonic development have elapsed, the best quality embryos are selected using the morphological assessment criteria (ASEBIR). Subsequently, the embryo transfer is performed to the gestational mother, followed by a pregnancy test[10].

Donor Selection

One of the most important decisions facing women in a couple is determining whether they will use an anonymous or known sperm donor. In Spain, for example, children born from donors do not have access to the donor's identity, as anonymity is in effect. This emphasizes the significance of considering local laws and regulations when making decisions in the assisted reproductive process. The choice may depend on personal preferences, values, and how the couple envisions communicating with the child about their genetic origin in the future[11]. Law 2006/14 on assisted reproduction techniques mentions that: “The choice of the sperm donor can only be made by the medical team that applies the technique, which must preserve the conditions of anonymity of the donation. Under no circumstances may the donor be personally selected at the request of the recipient. In any case, the corresponding medical team must try to guarantee the greatest possible phenotypic and immunological similarity of the available samples with the recipient woman"[12].

Just like in Spain, anonymity is also considered in the legislation of several European countries such as Denmark, Greece, the Czech Republic, Bulgaria, and France[11]. In South America, countries like Brazil, in resolution 2013/13 of the Federal Council of Medicine, also state that maintaining the anonymity of donors is mandatory, except for medical reasons that may require disclosure[13]. Likewise, Uruguay's Assisted Reproduction Act 19,167 of 2013, in its article 12, establishes that: "Gamete donation will be anonymous and altruistic, ensuring the confidentiality of the identity data of the donors"[12]. In Argentina, donation is generally anonymous, although under circumstances, the identity of the donor may be revealed[12]. In Mexico, it is also required that donor information regarding their identity be kept confidential[14]. On the other hand, more and more people born with IAD demand the right to know their biological origin[11]. Therefore, several countries have chosen to lift anonymity. Sweden, in 1984, was the first country to do so[11]. In 2005, the United Kingdom also lifted its anonymity and later countries such as Austria, Switzerland, the Netherlands, Norway, and Finland joined in[11]. Other countries, such as Iceland and Belgium, for example, contemplate a two-way approach in which donors are allowed to decide whether to remain anonymous[11]. There is a strong debate between revealing the identity of the donor or not, as some opinions affirm that the person born by this method has the right to know all the data related to the circumstances of his or her birth[11]; furthermore, as mentioned by Hayman, et al. In a study of 15 female couples in Australia, participants who chose a known donor did so because they considered it important that the child would have the possibility of fostering a relationship with the donor in the future[15]. The fact that this communication exists between the women of the couple and the children generates a closer bond of trust in the relationship and prevents the child from obtaining the same information in another way in the future, whether through third parties, conversations and/or family documents[11]. On the other hand, known donors have the possibility of providing support in medical circumstances such as organ donation and transplantation or simply serving as an additional caregiver[11].

Roles and Responsibilities in ROPA Method

Some women completely reject the idea of gestating and taking on that role in the partnership, despite their physiological ability to conceive[15]. However, in the context of ART for homosexual couples, when there is the same desire of both women to be a mother, the couple must make the decision as to which woman will be the surrogate. And in many cases that decision is difficult. One of the most important advantages that the ROPA method offers is allowing women to share biological motherhood, since both women can take an active role in the conception of the newborn. One of the women will be the egg donor and the other will be the recipient and gestate the embryos. However, the two women can play both roles; either at the same time, which is known as reciprocal ROPA, or after an unsuccessful cycle they can reverse the roles to try to improve results, which is known as reverse ROPA[16]. Women's personal desire to become pregnant is one of the motivations for sharing biological motherhood; Dondorp, De Wert and Janssens (2010) mention that the method can strengthen the bond between the couple or can improve the couple's sense of security in a complicated social environment, thus improving the couple's general well-being[17]. On the other hand, the ROPA method allows the couple to choose the partner with the best reproductive prognosis at ovarian and uterine conditions, potentially reducing obstetric risks[16]. Some medical indications for this method include poor egg quality, low ovarian reserve, or a higher genetic risk in one of the women, which may make her a suitable gestational mother[16,18]. Alternatively, if one of the women has a medical

condition that contraindicates pregnancy or prevents gestation, she could solely become the genetic mother[16]. Additionally, ROPA can be useful in cases involving transgender patients who underwent gender reassignment after fertility preservation[16].

Motherhood in Female Homosexual Couples

According to the 2000 U.S. Census, in at least 96% of municipalities, children are being raised in same-sex parent families[19]. Nationally, approximately 34% of female same-sex couples have children[19]. Mississippi (43.8%), South Dakota and Utah (42.3% each), and Texas (40.9%) are the states with the highest percentage of lesbian women raising children[19].

Conclusion

In recent years, the evolving concept of "family" has witnessed a transformation, with diverse family structures emerging in response to social, historical, and cultural shifts. Among these, same-sex families, particularly those consisting of female couples, have seen notable changes, thanks to advancements in assisted reproductive techniques (ART). The Reception of Oocytes from Partner (ROPA) method, a form of in vitro fertilization (IVF) where both partners actively contribute to the conception process, has gained acceptance among practitioners and patients.

This review explores the clinical, ethical, and psychosocial aspects of the ROPA method, shedding light on its advantages over other ART options for female couples. The ROPA method allows both women to play distinct yet vital roles in the reproductive journey, addressing the biological necessity faced by female same-sex couples seeking motherhood. The process involves controlled ovarian stimulation, IVF with donor sperm, embryo transfer to the gestational mother, and subsequent pregnancy.

The critical decision of selecting a donor—whether anonymous or known—is influenced by legal considerations and personal preferences. The review emphasizes the importance of understanding local laws, as anonymity rules vary among countries. The ongoing debate on donor anonymity reflects a balance between the right to privacy and the growing demand for knowledge of biological origins.

Roles and responsibilities in the ROPA method provide unique flexibility, allowing couples to share biological motherhood. The option for reciprocal ROPA or reverse ROPA, based on individual desires and medical considerations, adds to the method's appeal. Beyond enhancing the bond between partners, the ROPA method addresses medical indications, such as poor egg quality or higher genetic risk, offering a tailored approach to reproductive challenges.

In conclusion, the ROPA method represents a significant advancement in assisted reproduction for female same-sex couples, fostering inclusivity and providing a framework that aligns with changing societal norms. As acceptance grows, the ROPA method continues to contribute to reshaping the landscape of modern families, allowing for shared biological motherhood and personalized reproductive choices.

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The authors declare they have no conflict of interest

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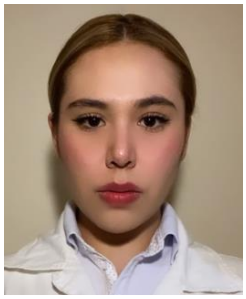
The symbiosis of diet, lifestyle, and fertility



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MANUSCRIPT

In an era where every morsel of food consumed and each lifestyle choice reverberates through our health, understanding their profound implications on fertility has never been more crucial. From the vibrant heart of Mexico, a nation steeped in a rich tapestry of culinary traditions and diverse lifestyles, springs forth illuminating insights into how these pivotal factors intertwine with the delicate threads of fertility.

Diet, an inextricable component of our existence, wield a formidable influence on reproductive health. The Mexican cuisine, a delectable amalgamation of diverse ingredients, presents both boons and banes in the fertility domain. Rich in fresh fruits, vegetables, and grains, it carries the essence of nutrients vital for enhancing fertility. However, an inclination towards processed foods and sugary beverages, often exacerbated by socioeconomic disparities, casts a shadow of nutritional imbalance, posing risks to optimal reproductive health.

Parallelly, lifestyle practices, ranging from physical activity to stress management, play a cardinal role. In the hustle of modern existence, nuanced by the unique cultural and economic landscapes of Mexico, lifestyle choices become pivotal harbingers of reproductive well-being or adversity.

Drawing from this, recommendations for bolstering fertility unfurl. A conscious embrace of a balanced diet, imbued with essential vitamins, minerals, and antioxidants, stands paramount. The embrace of traditional Mexican ingredients, such as beans, corn, and tomatoes, can be a cornerstone in nurturing fertility. Mitigating the consumption of processed and high-sugar foods is indispensable for curating a fertile environment within the body.

In tandem, fostering lifestyle practices conducive to reproductive health emerges as essential. Regular exercise, moderation in alcohol consumption, and adequate sleep are pillars supporting the edifice of fertility. Furthermore, navigating stress, a subtle yet powerful disruptor, through mindfulness and coping strategies, contributes profoundly to a fertile foundation.

As the realms of diet and lifestyle intertwine with the essence of fertility, a nuanced understanding and conscious application of their symbiosis become integral in the Mexican context, casting rays of hope and possibility in the journey of reproduction.

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Stress, Health and Well-being of Clinical Embryologists

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ABSTRACT

Clinical embryology is a demanding profession where the clinical embryologist is not only involved in the laboratory work with gametes and embryos but often a lot of logistic support. The pressures of timing, heavy workload, the monotony of procedures and the uncertainty of outcomes often creates a lot of pressures and stress on the embryologist. A stressed person is more likely to make errors, some can be insignificant while some can be disastrous like a mix-up or an accident. To add-on, long hours on the microscope can lead to soreness of muscles and joints leading to neck, back and shoulder pain. Physical pain with mental stress leads to discomfort and an unhealthy work environment. There are many publications on the burn out of health care professionals but not much is discussed about the health of an embryologist, a relatively new disciple. This paper discussed the various cause of stress in the life of an embryologist and also provides suggestions to overcome the same.

KEYWORDS: Stress, health, well-being embryologist.

MANUSCRIPT

Introduction

This massive growth of Assisted Reproductive Technology [ART] industry has led to a huge demand of ART professionals - mainly gynecologists - infertility specialists as well as clinical embryologists, the two pillars of ART. The clinical embryologists play a critical role in ART. They are involved in the processing of gametes, facilitating fertilization by insemination of oocytes or intracytoplasmic sperm injection (ICSI), culturing of embryos in vitro, cryopreservation of gametes and embryos, maintenance of the laboratory and culture conditions to facilitate development of healthy embryos, performing quality assurance assessment of the laboratory and interacting with patients. All this work is highly skilled and requires crucial decision making abilities. Furthermore, some of them also perform additional techniques like embryo biopsy for pre-implantation genetic testing (PGT) which need more refined training and skills. In some clinics, the embryologists are also involved in the administrative duties, data management and ensuring the timely supplies of disposables, perishable culture media and related products. All these responsibilities make clinical embryology a very demanding profession.

It is estimated that there are 1200 embryologist working in 4000+ IVF clinics in India alone [unpublished

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data] which leads to many clinical embryologists working at multiple locations in the same town or city or even other cities, across states, creating strains of travel. The situation possibly is not very different in other parts of the world as the need for clinical embryologists is on the rise.

There is a rise in the training and educational programs in clinical embryology worldwide. In the past one year, there are many publications which delve into the topic of training and educational programs on clinical embryology. However, the demands on the profession are currently very high[1,2].

To add on, ART cannot be considered to be a very effective procedure - as the desired outcome of healthy live birth - does not always occur in the first treatment cycle. The causes for the failure are innumerable ranging from age, cause of infertility, culture conditions, skills of the professionals involved and the still unknown reasons. However, in many clinics, the "needle of suspicion" points to the laboratory as not all Clinics have a healthy case discussion to determine the potential causes of failure. During personal discussions, embryologists have stated that despite meeting the laboratory Key Performance in the laboratory, the embryologists are questioned if all went well in the laboratory! This is another additional stressor for the embryologist.

Thus, all these conditions can create physical as well as emotional stress on the embryologist and could affect their work.

A few years ago, there was a report about the mix-up of embryos wherein one couples embryos were transferred to another patient where they implanted and resulted in a live birth[3]. There have been such reports in the past too and there may be some unreported on unnoticed incidents. The general public seemed scandalized how such an error could happen. As much as the 'mistake' seems unpardonable, we, working in do know that such a human error is not essentially due to callousness on the part of the embryologist but could be an outcome of work stress or fatigue.

Causes of such work-stress

Increased workload

As the demand for ART services increases, there is a shortage of skilled and knowledgeable clinical embryologists which would lead to increased workload for the existing embryologists. It has been reported that a high workload has 5.4 times greater odds for the incidence medication errors as compared to low workloads[4]. Although, no such data exists for clinical embryologists - it is possible that increased workload could be a potential cause for errors in ART.

To address this issue, professional bodies such as American Society of Reproductive Medicine have set up guidelines on the workload of embryologists[5]. However, it is not possible for all to follow these guidelines because of lack of available trained manpower. To address this need, many educational programs are being set up across the world[6]. In the last 2 years, 18 Universities in India have started a Masters clinical embryology programs in India to serve the demand for formally educated clinical embryologists. It still needs to be seen whether these programs would generate the trained, skilled manpower which were, till now, nurtured by mentoring programs[2].

Timing

Performing ART procedures at the right time is crucial for its success - be it follicular aspiration, denudation, insemination, ICSI, vitrification etc. Not performing procedures at the optimal time may affect outcomes. If there is a heavy workload, good time management and planning of the workload is essential to avoid situations of stress and panic, which can increase risk of errors.

Low Lighting

Although there is no data supporting the need for using low light in the ART laboratories, many laboratories still continue to use low light under the logic that in vivo the embryo grows in the dark working under diminished lighting[7]. Although scientific studies have provided low level evidence that low lighting affects work performance; there are reports that working in low light environment or lack of daylight exposure does affect the quality of life of workers[8,9].

The embryologist is compelled to spend hours at length in poorly lit environments which is turn may cause eye strain and fatigue and affect their quality of life. There are also concerns being raised on whether clinical embryologists would be deficient in Vitamin D if they have poor exposure to light. Funaki et al (2022 reported that 90% of the health care workers studied in a clinic in Tokyo were deficient in Vitamin D and attributed that to the long hours of indoor activity during medical care and daily life[10].

Repetitive tasks

Clinical embryology involves a lot of repetitive tasks, be it preparing dishes, changing the embryos into different wells during culture or vitrification-warming or ICSI. Manual repetitive tasks are known to be a source of human error in the laboratory[11].

Postural stress

A clinical embryologist spends hours stooped over a microscope. Despite good ergonomics, an

embryologist does experience strain on the back, neck and arms. A nationwide survey on the health of the embryologist carried out in Spain revealed that 44% of the embryologists experienced headaches sometime or often; 70% experienced neck pain - of which 15% experienced it all the time while 55% had it often or sometimes. 76% experienced back pain of which 18.6% had it all the time. 95% experienced arm pain of which 29% had it almost always and nearly 65% experienced it sometime or often[12]. The prevalence of musculoskeletal problems is high compared with that for working populations but similar to that observed for pathologists or microscopists (ranging from 76 to 57 %) [13, 14].

The study also reported lower mental health scores were obtained for women embryologists, embryologists who suffered headaches or pain in the neck or back, who suffered loss of visual acuity or who presented higher levels of emotional exhaustion or cynicism or lower levels of professional efficacy.

In a survey carried out on the occupational health issues experienced by UK embryologists, work-related ill health was self-reported by 58.3% of respondents, 76.2% of whom reported multiple issues. The most frequently disclosed ill-health conditions were musculoskeletal disorders (45.3%) and stress and mental health problems (27.8%)[15].

Although, there are no such reports from other parts of the world, there is no reason to believe why embryologists health would be very different in other countries.

Postural stress may not necessarily result in the loss of man-hours at work but can surely affect the quality of work and the laboratory workspace. A person in pain cannot be expected to be happy. This would in turn be reflected in their behavior with their colleagues and may even bring about an unhealthy emotional environment at home.

Preventing occupational health issues of clinical embryologists

1. Increasing the number of staff so that duties can be distributed.
2. Bringing about a rotation in the work being carried out so that the monotony can be broken.
3. Ensure weekly holidays. Sometimes, embryologists need to come to just pre-incubate media even on holidays. If the work can be planned such that the embryologist can get a total off.
4. Documentation and paper-work is a crucial and integral part of an embryologists' work. However, if automated systems can be developed then this pressure can also be reduced on embryologists.
5. Embryologists can be asked to take a few minutes off after procedures to get some fresh air if possible or at least perform some simple exercises to release the back. The ancient Indian science of yoga does offer simple yogic postures which can even be done at the workplace to overcome the musculo-skeletal problems such as neck and low back pain. Modern studies have also provided evidence on its efficacy. Williams et al (2005) Pain 115: 107-117; Journal of pain 30:2012
6. Embryologists need to have some hobbies or sport; be it music, art, yoga, hiking - something that can help refresh their body and mind.
7. A healthy work environment is necessary. It is advisable to have managers or senior management who are from the field of ART so that they can relate to the work and thereby set realistic expectations.

Burnout

Burnout is a reality among medical professionals. Burnout by definition is a reaction to prolonged stress that may include emotional exhaustion, cynicism, and a lack of satisfaction from work. Medscape carried out a survey in 2022 among 13000 physicians across various specialties on physician burnout and depression. They reported a burnout rate of 40 to 50% across the physicians surveyed and this was irrespective of the pandemic. One of the 5 physicians even considered leaving the profession[16]. Although burnout has not been reported or studied in clinical embryologists - it does not mean that it does not exist.

Conclusions

A healthy embryologist therefore is not just the one who does not miss a days work because of ill health but one who is physically fit, emotionally balanced mentally sharp and alert with clarity in thought to take the right decisions.

It is time to reflect and act on the health and well-being of embryologists as they are not only responsible for the current but also future generations too.

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CONFLICT OF INTEREST

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