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Positive Outcomes of Ozone and NAD Therapy in Infertility Treatment: A Retrospective Observational Case Series

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ABSTRACT

This retrospective observational case series aims to delineate the positive effects of ozone and NAD therapy on patients dealing with infertility. Conducted at First IVF Fertility Centre, the study examined six female patients who had previously experienced multiple IVF failures. We meticulously analyzed these cases, noting remarkable improvements following the integration of alternative therapeutic modalities, particularly ozone therapy, into their treatment regimens. Each of the six cases demonstrated a discernible positive outcome, characterized by the acquisition of euploid, transferable embryos or successful pregnancies. The findings suggest that the integration of ozone and NAD therapy can significantly benefit patients dealing with infertility. To comprehensively ascertain the impact of these alternative therapies, a rigorous evaluation, such as a randomized pilot study, is recommended. This empirical approach would empower patients and healthcare providers to make well-informed decisions regarding the potential benefits and associated risks of these innovative treatment avenues, fostering a proactive and collaborative approach to fertility care and ultimately enhancing patient outcomes.

INTRODUCTION

Infertility is one of the prevailing global concerns that impacts millions of couples worldwide (Obeagu *et al.*, 2023). In this context, In Vitro Fertilization (IVF) stands as a miracle of modern medication for couples grappling with conception challenges (Inhorn, 2021). Assisted reproduction involves multiple complex steps, from ovarian stimulation and egg retrieval to fertilization and embryo transfer. Despite advancements in IVF techniques, a subset of patients confronts the disheartening reality of recurrent IVF failures, often attributed to factors such as inadequate embryo development leading to the absence of viable blastocysts for transfer (Fodina *et al.*, 2021). This subset poses a formidable challenge within the realm of fertility treatment. This phenomenon not only leads to emotional distress for couples but also emphasizes the need for alternative approaches to improve IVF outcomes (Wu *et al.*, 2023). Emerging as an innovative medical intervention such as ozone therapy or Nicotinamide adenine dinucleotide (NAD) therapy may have the potential to enhance IVF success rates and revolutionize the landscape of fertility treatment (Merhi *et al.*, 2019).

Medical advancements have highlighted the connection between free radicals and various diseases. Therefore, the chances of developing various diseases due to stress are increased by a lifestyle, exposure to chemicals and pollution, smoking cigarettes, using drugs, experiencing illness and dealing with stress (Pădureanu *et al.*, 2022). Antioxidants are substances that can counteract the effects of radicals and reduce the occurrence of damage

caused by oxidative stress. One of the causes of infertility is inflammation (Ravel *et al.*, 2021; Yuxin *et al.*, 2021) and Ozone therapy, a therapeutic approach utilizing a mixture of ozone and oxygen, has garnered attention due to its potential to modulate oxidative stress, enhance circulation, and stimulate tissue regeneration (Scassellati *et al.*, 2020).

These ozone therapy attributes are promising for addressing the challenges posed by repeated IVF failures. Oxidative stress and inflammation have been linked to impaired embryo development and implantation, which are critical factors in IVF success. Ozone therapy's ability to mitigate oxidative stress and promote tissue repair could contribute to a more favourable uterine environment for embryo implantation (Escandón *et al.*, 2020).

NAD has grown beyond its role in metabolism to become a crucial regulator of various physiological processes. These processes include DNA repair, autophagy adaptive stress responses, maintaining stability and ensuring cell survival (Srinivas *et al.*, 2019). Notably, studies have indicated that NAD⁺ levels decline with age in tissues and are associated with age-related diseases (McReynolds *et al.*, 2020).

The inclusion of alternative therapies as an adjunct to standard IVF treatment represents a novel avenue for addressing the unmet needs of patients with recurrent IVF failures (Dias *et al.*, 2023).

MATERIALS AND METHODS

This case study was designed using a retrospective and systematic approach to evaluate the potency of

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adjunctive therapies of ozone and Nicotinamide adenine dinucleotide (NAD) sessions in improving IVF outcomes among women experiencing recurrent failures (Moreira, 2021). Before starting this study on patients, approval from the Institutional Review Board (IRB) was obtained, ensuring compliance with ethical guidelines and protecting participant rights. Subsequently, patients with documented recurrent IVF failure history were carefully selected for inclusion in the case series, with all participants providing informed consent prior to their involvement.

The patients' ages ranged from 29 to 43 years. They had underlying causes of infertility, including diminished ovarian reserve and endometriosis. Detailed data on the six participants' IVF treatment history, past failures and outcomes, were meticulously collected and analyzed. Then, therapies and their frequency and dosage were systematically integrated into treatment regimens with standardized protocols for five to eight sessions per patient. Strict quality control measures and staff training guaranteed data accuracy and reliability. Patient responses to the integrated treatments were observed and evaluated to identify potential advancements, utilizing statistical analysis techniques to assess efficacy. Treatment outcomes, including acquiring transferable embryos or successful pregnancies, were compared to previous IVF attempts. Individual case conclusions were drawn to provide insights into the potential efficacy of ozone and NAD therapy in addressing recurrent IVF failures.

RESULTS AND DISCUSSION

Results

The results of this case study are presented as a series of case studies, each highlighting the outcomes of integrating alternative approaches, ozone and NAD therapies. The following findings elucidate the potential efficacy of these therapies in making IVF successful and also the challenges faced by patients seeking successful pregnancies.

Case Studies

The first case was of a 29-year-old woman, married, with a history of primary infertility, who carries genetic traits for autosomal recessive blindness and Thalassemia. Her AMH (Anti-Müllerian Hormone) level register was 2.93 ng/ml. Having undergone seven prior IVF cycles elsewhere, she encountered a lone embryo transfer that yielded no pregnancy. Following three intravenous and one vaginal ozone session, she embarked on an IVF cycle that led to the development of a normal (euploid) embryo and resulted in a successful pregnancy after embryo transfer.

In the second case, a 42-year-old woman experienced secondary infertility and an AMH level of 1 ng/ml. After three previous IVF cycles that led to aneuploid embryos, she integrated antioxidant sessions, including 11 sessions of NAD, and underwent eight intravenous ozone therapy sessions. Two subsequent IVF cycles ensued, one yielding a single euploid embryo.

Thirdly, a 41-year-old woman with secondary infertility, endometriosis stage IV, and an AMH level of 0.07 ng/ml underwent multiple unsuccessful IVF cycles. Upon beginning five sessions of NAD and five sessions of intravenous ozone therapy, her subsequent IVF cycles showed a significant shift in outcomes. One cycle resulted in a genetically normal embryo and a successful embryo transfer, leading to a positive pregnancy.

In the fourth case, a 41-year-old woman in her third marriage, without prior children, confronted poor ovarian reserve (AMH: 0.2 ng/ml). Three prior IVF cycles yielded abnormal embryos. Following two NAD sessions and five intravenous ozone therapy sessions, she underwent two IVF cycles, each resulting in a single euploid embryo, thus marking a noteworthy improvement.

In the fifth case, a 41-year-old woman with primary infertility and an AMH level of 0.35 ng/ml underwent eight IVF cycles, producing aneuploid embryos with just one normal embryo. After seven intravenous ozone

Table 1: Summary of case series

Case	Patient's Age	Diagnosis	Previous IVF Cycles	Alternative Therapies	Outcomes
1	29	Primary infertility, autosomal recessive blindness, Thalassemia	7	3 IV + 1 vaginal ozone	Successful pregnancy
2	42	Secondary infertility	3	11 NAD + 8 IV ozone	1 euploid embryo
3	41	Secondary infertility, endometriosis stage IV	Multiple	5 NAD + 5 IV ozone	1 euploid embryo, successful pregnancy
4	41	Poor ovarian reserve, no prior children	3	2 NAD + 5 IV ozone	2 euploid embryos
5	41	Primary infertility	8	7 IV ozone	2 euploid embryos, successful pregnancy
6	40	Secondary infertility, previously a miscarriage	6	5 NAD	2 euploid embryos, successful pregnancy

sessions, two IVF cycles ensued, each yielding a euploid embryo. A successful transfer led to a positive pregnancy outcome.

The last case was a 40-year-old woman experiencing secondary infertility who had a miscarriage from a spontaneous pregnancy. Her Anti Hormone (AMH) level is 1.27 ng/ml. She underwent six rounds of in vitro fertilization (IVF), and all the embryos produced in these cycles were abnormal due to aneuploidy. After receiving five sessions of NAD (each containing 250mg of NAD) as advised by her physician, she decided to try another IVF cycle that led to two euploid embryos being successfully transferred, and pregnancy occurred.

Table 1 summarises each case, including age, previous IVF Cycles, alternative therapies used and outcomes achieved.

Discussion

The cases presented in this series highlight the potential benefits of incorporating antioxidant therapies, specifically Nicotinamide adenine dinucleotide (NAD) and intravenous ozone sessions, into the treatment protocols of women facing infertility challenges (Dias *et al.*, 2023). These cases underscore the importance of individualized care and the exploration of innovative approaches in assisted reproductive medicine (Sunderam, 2019). Antioxidant therapies appear to have played a pivotal role in enhancing the quality of embryos, resulting in genetically normal embryos available for transfer. NAD and intravenous ozone therapy emerged as valuable adjunctive treatments, contributing to the overall success of the IVF cycles, evidenced by the development of euploid embryos and successful pregnancies (Hussain *et al.*, 2021; Sunderam, 2019).

In reviewing the literature, it is evident that there is a growing trend towards the use of alternative medicine (AM) in treating infertility, challenging traditional therapies. However, some randomized controlled trials (RCTs) have shown that complementary and alternative medicine (CAM) does not consistently impact infertility, and there remains no consensus on its mechanism of action on fertility. (Saha *et al.*, 2021; Sharifi *et al.*, 2021)

Nevertheless, therapies such as ozone therapy have shown promise in enhancing aspects of reproductive function, including clearing blockages in the fallopian tubes, protecting against infections, and potentially reducing damage to the ovaries while improving ovarian reserve. The potential of ozone therapy to reduce inflammatory responses and adhesions suggests its value as a component of IVF treatments. (Dias *et al.*, 2023; Merhi *et al.*, 2019)

Additionally, the decline in NAD availability with age significantly impacts egg quality and overall fertility, highlighting the potential of NAD supplementation as a therapy for addressing infertility challenges associated with ageing. Future research targeting women with repeated miscarriages, poor responses to IVF treatments, endometrial lining problems, or decreased ovarian reserve

is warranted to further elucidate the effectiveness of alternative therapies in complex infertility (Wu *et al.*, 2019). Moreover, each patient in this case series presented a unique clinical profile. Therefore, findings from this discussion underscore the importance of a personalized approach to treatment and the exploration of innovative therapies in addressing complex infertility cases and innovation in the evolution of personalized medicine in reproductive health. Further research is needed to understand alternative therapies' mechanisms of action and efficacy in improving fertility outcomes.

CONCLUSION

Incorporating ozone therapy and complementary treatments reflects a comprehensive strategy for tackling intricate infertility cases, potentially paving the way for advancements in fertility treatment outcomes.

While these instances offer encouraging glimpses into the potential advantages of antioxidant therapies, additional research is necessary to confirm their effectiveness and safety. Furthermore, further investigation is needed to elucidate the exact mechanisms through which NAD and intravenous ozone therapy can impact embryo development. Ongoing research and broader-scale studies are imperative to validate these findings and enhance treatment protocols in reproductive medicine.

Data Availability Statement

The data supporting the findings of this study are stored in software called MEDITEX, which is designed specifically for In Vitro Fertilization (IVF) clinics. MEDITEX serves as a tool for managing and documenting patient data within Assisted Reproduction organizations. However, it's important to note that there are restrictions on accessing this data due to licensing agreements for this study. Therefore, provided database was retrieved from MEDITEX Internal Data Management System and cannot be accessed publicly. Nevertheless, the authors of the study are willing to access to the data upon request. The data and materials used in this case series are available upon reasonable request for transparency. Access requests should be directed to the corresponding author.

Abbreviation List

In vitro fertilization (IVF); Anti-Müllerian hormone (AMH); Nicotinamide adenine dinucleotide (NAD)

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