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Research Article

Case Report of Successful IVF with Pregnancy of a 46 Year Old Lady after 12 Years Trials and 10 failed IVFs

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Abstract

Background: In this study, we indicate the importance of a case, where specific diagnostic tests such as NK level, NK endometrial cells, NK activity, embryotoxicity (ETA), and PLA (platelet leukocyte aggregates) were used for investigating infertile women with many failed IVFs.
Case presentation: We describe a very important case of unexplained infertility, where a 46 year old lady managed finally to get pregnant after 12 years of consecutive trials and 10 failed IVFs. Our center tested her for all 3 NK markers, ETA, and Vitamin D3, TSH, and PLA, which are essential for positive pregnancy. The lady was treated with intravenous solution of intralipid after the high NK result. She was administered with two dosages and then performed embryo transfer where after 10 days she received the positive pregnancy test result.
Conclusion: The high evaluation of immune status based on the specific tests of NK panel (all 3 markers), ETA, and PLA can save time and money for couples that have attempted several embryo transfers in IVF centers with unsuccessful pregnancies. Also, the targeted individualized treatment of the couple can significantly increase the chances for successful pregnancy.

Key words: NK cells, ETA, IVIg intralipid, failed IVFs, infertility

Background

Immunological individualized and specific targeted testing in one of the most necessary approaches in order to diagnose unexplained infertility, rapid spontaneous abortions (RSAs), and failed IVFs [1-2]. Despite the scientific achievements, the last decade some innovative markers were discovered to help for the successful implantation of the embryo, although many IVF centers don't take advantage of them. One reason could be because different IVF centers may use different definitions for repeated implantation failure (RIF) [3]. The other reason is the oppositions among reproductive immunologists in different markers, which confused the specialized individuals with a false advice that leads to the couple to unsuccessful pregnancy [4]. However, significant immunological markers that changed the era in reproduction and assisted in successful pregnancies in many couples have been reported some years ago. These markers included antiphospholipid antibodies (APA); lupus anticoagulant (LA); thyroid-thyroglobulin and microsomal antibodies (TGT); embryo toxic factor (ETA); and systemic CD56+/CD16- cells (NK cells) [5, 6]. In this case, the confusion and lack of knowledge from the different IVF centers and gynecologists led a 46 year old lady to visit our center after 12 consecutive years for trying by different assisted reproductive technologies.

Case presentation

A 46 year old lady visited our center with her 52 year old husband with at least 12 year infertility medical record. The lady was submitted in laparoscopic surgery for endometriosis at 2007, and additionally she performed laparoscopic surgery and removed the right salpinx at 2010. Then, a year later the left salpinx was removed respectively. Also, the thickness of the endometrium was measured by Ultrasound to be 9.5mm.

The couple has started attempts for pregnancy since 2008, and they had their IVFs trials from 2011 until May 2016 (total 10 IVF trials). After all these years of continuous attempts, they never had a successful pregnancy. So, they heard about our center and wanted to exhaust their last chance so they would not let down their dream to have a baby.

Their next step according to our guidance was to do our specific individualized immune tests. The lady was tested initially for inhibin B, which was low (32.5pg/ml) and decided to go with donor egg in the 11th IVF trial. Then, she lady was tested for the NK panel {total NK cells ($CD3^-CD56^+$), endometrial NK cells ($CD3^-CD16^-56^+$), and NK activity}. Also, Platelet-leucocyte-aggregates {PLA ($CD41a^+CD11b^+$} test was performed and this marker was high too **(figure 1).** We explained the couple that NK was the major reason for their failed implantation in correlation with the high PLA, and we planned therapeutic strategy in order to regulate the NK cells and go to next IVF trial with much higher chances for successful pregnancy. On the other hand, Husband's sperm analysis and DNA fragmentation were fine (not reported), while the levels of Vitamin D3 of the lady were low and we administered oral supplement of Vitamin D3 (25000 iu/ml) called lecalcif, and baby aspirin day after day because of the high PLA marker.

Diagnostic markers	3 months before Embryo transfer	1 week before embryo transfer	Reference ranges
$CD3^{-}CD56^{+}$	12%	9%	2-13%
$CD3^{-}CD16^{-}56^{+}$)	27%	12%	6.5-13.5%
NK activity	9.5%	8.5%	N<10%
ETA (embryotoxicity)	negative	negative	negative
VitD3 (25OH)	18.5 mg/ml	32.8 mg/ml	N>20 mg/ml
TSH	1.9 μIU/ml	1.8 μIU/ml	0.34 - 2.5 μIU/ml
PLA ($CD41a^{+}CD11b^{+}$)	3.5%	1.45%	1.07-1.56%

Figure1: Values of Specific diagnostic markers 3 months before the embryo implantation and 1 week before embryo transfer after intralipid treatments of NK panel, lecalcif, and baby aspirin.

Based on the diagnostic result, 2 dosages of 10 ml (of 20% intralipid (Fresenius Kabi, India) diluted in 0.9% NaCl 250ml solution) were administered intravenously before the embryo transfer in order to regulate suitably the NK cells for the next IVF trial. Then, immediately blood sample was taken to test again all markers one week before the embryo transfer (figure 1). Then, the process of embryo transfer of 2 embryos followed and after 10 days a **positive pregnancy test** was detected for the **FIRST TIME** after so many years. Then a final dosage of intralipid was administered after the positive pregnancy test, so the danger of miscarriage could be limited down at the first trimester of gestation [7]. At the first ultrasound examination, one embryo was detected with positive heart beats and pulses. Later, the nuchar translucency screening was followed, level 2 ultrasound was performed, and the pregnancy continued normally without any problems. The baby was born at November 2017 with total 3100gr in very good health condition.

Discussion

The efficacy of IVFs depends on a specific testing and evaluation of the genetic material of the couple plus the immune status of the wife. DNA fragmentation of the sperm is one marker for the male sperm quality and inhibin B is female marker for the female's quality of egg [8, 9]. Then major markers that play important role for pregnancy are vitamin D3 which has to be adequate and TSH that has to be below 2.5mIU/L [10, 11and12]. The specialized targeted immune tests seem to make the difference and increase the chances for successful IVF trial, and specifically in this case endometrial NK cells, which were lowered in normal range by the administration of intralipid solution before embryo implantation. NK levels, NK endometrial levels and NK activity are crucial markers for successful pregnancy, miscarriages (RSAs), and failed IVF trials [13-15]. On the other hand, there are studies that don't support the important of NK cells in the outcome of IVF trial [16. 17], but our 15 year experience in this field proved the opposite, and has majorly assisted in important pregnancies like this present study case that wouldn't conceive in the future. The regulation of NK cells with the specific amount of intralipid administered intravenously was one of the novel innovation treatments because of no side effects. This treatment has assisted significantly in women that had increased NK cells or high activity and had many failed IVFs or miscarriages [18-19]. On the other hand, it must be stressed that the dosages of intralipid must be ONLY administered by reproductive specialists and must be accompanied ONLY by specific diagnostic tests because high dosages and not diluted with NaCl solution could contribute to the opposite result, which could be the rise of the NK cells and their activity. Moreover, it has been reported that high dosage of intralipid can cause a series of serious adverse effects such as acute **kidney injury, cardiac arrest, acute lung injury, venous thromboembolism, fat embolism, fat overload syndrome, pancreatitis, allergic reactions and increased susceptibility to infection [20].**

Conclusion

The administration of intralipid **MUST** be performed **ONLY** by specialists, who MUST have the knowhow and experience in clinical and laboratorial issue of NK markers **(total, endometrial NK, and activity of NK cells).** On the other hand, the infertile couples should search very carefully the fertility centers that not just to perform an IVF trial by the standard protocol, but to carefully test for their genital status to be of high quality before any IVF trial. They should also receive the right consultation from experts in reproductive medicine with high morale and deontology so they avoid any financial damage and psychological trauma.

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