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Research Article

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Role of Low Dose Intravenous Immunoglobulin in IVF Failure - A Retrospective Analysis

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Abstract

Background: *In developing countries the number of in vitro fertilization (IVF) attempts is often limited by the high costs of the procedure and relatively low success rates. In such a setup we have tried to evaluate the effect of low dose intravenous immunoglobulins (IVIg) administered to patients who have had previous failed IVF outcomes. Bearing in mind that the inherent fecundity of Indian population is higher and thus a lower dose of IVIg may suffice to give positive outcomes at an affordable price, in this manner providing them with the possibility of affording more attempts if required.*

Objective: *To evaluate the role of low dose intravenous immunoglobulin in IVF failure.*

Design: *Retrospective analysis*

Materials and methods: *This is a retrospective study beginning from 1st January 2014 till 31st December 2014. During this period, 124 patients with two or more failed IVF cycles were included. The controlled ovarian stimulation was started on cycle day 2 using gonadotropins (225 - 450 iu daily) and GNRH antagonist was added on the day when follicle reached 13 -14 mm. When follicles reached 18mm, transvaginal ultrasound guided oocyte aspiration was performed within 36 hours of the hcg trigger. On the ovum pick up day, 5 grams IVIg was administered to the patient as a slow infusion. Embryo transfer was done on day 2 or 3. Serum beta hcg was done 14 days after the embryo transfer and pregnancy rate and clinical pregnancy were evaluated.*

Results: *The total pregnancy rate was 46% (57/124) and clinical pregnancy rate was 42.7% (53/124).*

Conclusion: *Our study concluded that low dose IVIg may play a significant role in improving pregnancy rates in women with previous failed IVF attempts.*

Keywords: Recurrent IVF failure, implantation failure, IVIg

Background

Since the advent of ART, there has been a ray of hope for couples unable to conceive on their own or with slighter forms of assistance. Despite several crucial advancements, the ever-elusive implantation failure has not yet been completely understood thus a lucid explanation has yet to be found.

Natural killer and NKT-like cell (CD3+CD56+CD16+) activity is considered to be among the key factors for reproductive success. In the absence of immunological screening, positive outcomes using high doses of intravenous immunoglobulin (IVIG) prior to ovum pick up, following embryo transfer as well as post conception in preventing recurrent reproductive failure (RRF) have been reported in several studies.

Here, we analyze the influence of Low dose IVIG on pregnancy success in women with RRF in order to find a dose low enough to ensure financial feasibility for our community of patients and substantial enough so as to be effective in the manner in which it is intended. One of the premises being that the Indian population with its lower Body mass indices and inherent fecundity may respond to a lower dose of immunoglobulin G.

Materials and methods

This is a retrospective study beginning from 1st January 2014 till 31st December 2014. During this period, 124 women with 2 or more IVF failures were included in this study. The couple's past management protocols were reviewed comprehensively and they were physically examined. Husband's semen analysis was performed, all relevant blood investigations of the couple such as AMH, FSH, LH, Prolactin, TSH, general blood investigations, detailed USG of

the woman were done in order to rule out other possible causes of IVF failure. When none were observed the study proceeded in the manner described hence.

After careful selection of patients, controlled ovarian hyper stimulation (COH) was started using Gonadotropins in the individualized dosage according to patients profile (225IU-450IU). Regular ultrasound exams were performed in order to assess ovarian follicular response to the stimulation and adjustment of gonadotropin doses was made accordingly. When the follicles reached 13-14mm in size, Antagonist injections were started and continued till the size of the follicles reached 18mm, when trigger was give using recombinant HCG.

Prior to the oocyte pickup, 5 grams of IVIG was given as a slow intravenous infusion. Within 36 hours of the HCG trigger the Oocyte pick up was done. Embryo transfer was done on Day 2-3 following pick up. 2 weeks after embryo transfer, serum beta HCG levels were analyzed in order to ascertain pregnancy status and thereafter-clinical pregnancy rates.

Results

46% out of the 124 women selected for the study had Serum Beta HCG levels which were positive for pregnancy. Of these women 42.7% went on to have a clinical pregnancy.

Hence our study shows that a high dose IVIG protocol is not always required to have a significant pregnancy rate. In fact, it would seem that these doses maybe open to individualization, although further studies need to be done in that regard. With this protocol significantly decreasing the financial load on the patient, they will still have a fair chance of overcoming previous IVF failures and even leave open an option for further attempts at IVF/ICSI if need arises.

No adverse effects were observed in any patient during the course of this study.

Discussion

Since the first use of parenteral immunoglobulin in 1935, for measles, immunoglobulins have since served mankind well in the treatment of several autoimmune and inflammatory diseases such as a gammaglobulinemia, ITP, Kawasaki syndrome, Guillian Barre syndrome etc.

IVIG is a poly-specific immunoglobulin prepared from the pooled plasma of thousands of healthy donors. Recently the role of Natural Killer cells in the process of reproductive medicine has been brought to light, in patients with IVF undergoing embryo transfer.

Recurrent IVF failures with chromosomally normal embryos have been attributed to an excess of proimflammatory Th1 type cytokines as compared to Th2/3 cytokines [1]. Altered homeostasis due to deficiency or defective function of CD4+,CD25+, Fox P3+ regulatory T cells is also common in several autoimmune diseases [2]. The use of IVIG is believed to enhance the suppressive effects of these regulatory T cells hence leading to remission of autoimmune and inflammatory diseases and even better IVF outcomes.

Increasing evidence directs our attention towards the role of Natural Killer (NK) cells as an immunological component of normal pregnancy. Belonging to the innate immune system, they play an important role in maternal tolerance to the semi-allogenic fetal tissue by promoting angiogenesis, spiral arterial remodeling, trophoblastic invasion [3]. Recent molecular studies on mechanisms of implantation failure and miscarriages have shown a common pathogenic pathway suggesting that these two conditions represent different points on a spectrum that can be termed reproductive failure [4]. NK cells play a key factor in this pathway [5].

Owing to its high cost as well as the high customary dosage which is not a feasible option in our study population we opted for a lower dosage in order to find the lowest possible dosage of IVIG which will produce the anticipated benefactorial effect on patients with repetitive IVF failures and thus used 5grams parenteral IVIG infusion per patient prior to Ovum pick up.

A significant increase was observed in the overall positive pregnancy rates and clinical pregnancy rates at this low dose which benefits our fiscally frail patients and permits them to have a renewed chance with a genuine opportunity for success after multiple IVF disappointments.

Previous prospective studies done by Stricker, et al. 2000 on the effect of low dose IVIG in women with immunologic abortion showed that a low dose IVIG of 0.2g/kg body weight given 2 weeks within attempted conception as well as on a monthly basis throughout pregnancy till 30weeks of gestation proved to increase the pregnancy rates, especially in older women [6].

The study did concede however that the optimum duration of the treatment had yet to be determined. Studies done by Elram, et al. in 2005, where 2 IVIG doses of 30gms each were given to the patients of recurrent IVF failures (defined in the study as couple with 7 implantation failures after IVF), one before oocyte retrieval and once as soon as fetal pulse was detected, showed that patients with recurrent IVF failures and similar HLA, may benefit from IVIG treatment [7].

A dosage of 400mg/kg body weight prior to Embryo Transfer as well and every three weeks thereafter if clinical pregnancy was attained was used as a protocol by Moraru, et al. 2012, in a cohort of Spanish women with RIF. It was then found that there were significantly high clinical pregnancies as well as live birth rates [8].

A prospective study of young (<38 years) women with infertility and T helper 1/T helper 2 cytokine elevation conducted by Winger E, Taranissi M, Toukhy T, Ahuja S, Reed J, Ashoush S, published in 2008 concluded that the use of a TNF-α inhibitor and IVIG significantly improves IVF outcome in young infertile women with Th1/Th2 cytokine elevation [9].

Thus we find that the role of IVIG in improving the success rates of IVF in women with RIF of unknown etiology associated with expansion of NK and NKT-like cells is nearly undisputed [10]. The dosage however cannot quite be standardized and studies like ours will aid in the establishment of the dosage range depending on each patient. Thus patients with limited resources in developing nations need not deprive themselves of an opportunity to complete their family and lives.

Conclusion

Low dose IVIG therapy seems to be helpful in patients who have previous failed IVF cycles currently undertaking IVF improving implantation rates and pregnancy outcomes [11].

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