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THE ROLE OF IMMUNOTHERAPY IN UNEXPLAINED RECURRENT ABORTION. A CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Recurrent abortion refers to failure of pregnancy of three or more pregnancies with the same partner with the incidence of 1 % of the pregnancies. Many modalities of treatment are available for the management but the role of immunotherapy needs more exploration. Due to high cost and less knowledge of such therapy such modality of treatment is still under exploration. No guidelines have been set for their use in the management of recurrent abortion. With the case report we will bring about a successful outcome of G5 A4 of recurrent abortion managed with immunotherapy at our institute. This article will also include reviewof literature regarding the type, dosage and the effectiveness of immunotherapy in the management of recurrent abortion.

Keywords: Recurrent Abortion, Ivimmunoglobulin, Successful Outcome, OGTT: Oral Glucose Tolerance Test.

Abbreviations: IV: Intravenous, IG G: immunoglobulin, FGR: Fetal growth restriction, CD: cluster of differentiation, Dand C: Dilation and curettage, LSCS: lower segment caesarean section.

INTRODUCTION

Recurrent abortion accounts for 1%of all pregnancies and the aetiology is unclear in 68%.[1]The use of ecosprin and low molecular weight in prevention of recurrent miscarriage has been studied and found useful in cases of idiopathic recurrent miscarriage.[2]Regarding the role of IVImmunoglobulin in management of recurrent abortion remains a matter of exploration. IV immunoglobulin increases peripheral CD 3 and decreased CD 8 count and prevents pregnancy loss by working on the immunological factors of recurrent abortion. Immunological factor plays a role in recurrent abortion and is generally a diagnosis of exclusion.[3] More than 60% of recurrent spontaneous abortions are caused by immune system disorders and 80% are closely related to immune factors. Intravenous immunoglobulin belongs to passive immunotherapy and regulates cytokines secreted by lymphocytes, block immune response and cytotoxicity by using antibodies in immunoglobulin.[4] This case report will highlight the role of immunotherapy in the successful management of idiopathic recurrent abortion and also bring insight on the available literature.

Case Report:

A 33-year-old G5 A4 came at 6 weeks of pregnancy with history of recurrent abortion for further management. Her obstetrics history -married for 10 years. Her first pregnancy was confirmedby ultrasound and patient underwent medical abortion in

2013. Her second pregnancy was in 2017 was a spontaneous conceptiondiagnosed as missed abortion at 8 weeks managed medically. Her third pregnancy was a spontaneous conception in 2019 diagnosedagain as missed abortion at 8 weeks. D and C was done.

The patient presented to our centre in her fourth pregnancy at 8 weeks. On examination she had acanthosis nigricans at neck andpale skin over palms and soles and it also resulted in spontaneous abortion at 8 weeks. D and C was done and the products were sent for micro array and the results were negative.Parental karyotyping was carried out and it was negative in both partners. OGTT and HBA1C were normal.APLA serology and lupus anticoagulants were negative.On further probing, a history of ankylosing spondylitis in the husband was elicited and he was tested for HLA loci and HLA B-27 came out to be positive.

The husband's DNA fragmentation index (DFI) was 22%.This prompted investigation for immunological cause in the patient and her HLA gene mapping was done.No cause of recurrent abortion was found hence decisionwas taken to use immunotherapy in the next pregnancy. She conceived after 2 months of taking IV immunoglobulin. It was her fifth pregnancy and was confirmed by pregnancy test and ultrasound. IVimmunoglobulin 400 mg/kg (15 gram) was started under supervision of immunologist and continued every month in the same dose till 20 weeks of pregnancy. She was also put on ecosprin 75 mg which was continued till 34 weeks and intramuscularprogesterone depot 250 mg preparation till 16 weeks. She was diagnosed with hypothyroidism at 8 weeks,Thyronorm 25 mcg was started for the same. The pregnancy was monitored at regular intervals and serial obstetrical scans were done. Patient did not develop any side effects due to administration of immunoglobulin therapy. Her level 1 and 2 scan were normal and no FGR was detected at any stage. At 28 weeks of gestation,she developed gestational diabetes which was managed metformin 500 mg. At 38.4 weeks of gestation patient had emergencyLSCSin view of decreased fetal movement with non-stress test showing fetal tachycardia and ultrasound in the last trimester suggestive of single loop of cord around the neck.A healthy female baby of 3.3kg was delivered. Her post-op recovery was well.

REVIEW OF LITERATURE

Habets.et al. (2022) conducted a systematic review and meta-analysis to evaluate the effectiveness of IVIG treatment on pregnancy outcomes among women with three or more pregnancy losses with a known immunological cause. A total of 8 studies were included showed an increase in the live birth rate in women receiving IVIG for recurrent pregnancy loss with a relative risk ranging between 1.93 to 8.64. The meta-analysis also corroborated the findings concluding that a live birth was twice more likely in women receiving IVIG. A sub group analysis evaluating the timing of intervention was also performed by dividing the studies into 2 groups, one receiving IVIG prior to conception and the other after conception.

However, this was not statistically significant with p value 0.266.[5]In a study published in the Lancet in June 2022, women with primary RPL with four or more unexplained pregnancy losses received 400mg/kg IVIG or placebo for 5 days at a stretch starting from 4 to 6 weeks of gestation in a double blind, randomised fashion from June 2014 to Jan 2020. The results were extrapolated as ongoing pregnancy rate at 22 weeks

and live birth rate. Both these outcomes were significantly higher in the IVIG group as compared to placebo, 62% vs 34.7% (p = 0.009) and 58% vs 34.7% (p = 0.03) respectively. Further, favourable outcomes were more in the women who received IVIG at 4 to 6 weeks as compared to 6 weeks period of gestation onwards.[6] In our case alsolow dose immunoglobulin therapy was given once a month prior to conception and continued upto 20 weeks of pregnancy with favourable outcomes.Systematic reviews published suggest that medium dose IVIG treatment is effective in womenRPL but some studies have not found any added advantage.[7]A similar meta-analysis was undertaken by Shi et.al to study the efficacy of intravenous immunoglobulin in the treatment of recurrent spontaneous abortion. 15 articles including 902 patients were included from all RCTs listed in PubMed, Cochrane library and Embase till august 2021. It was concluded that IVIG can increase the live birth rate in patients with recurrent spontaneous abortion (p value = 0.02).[8]

In our case we started the medium dose IVIG at the time of confirmation of pregnancy and continued up to 34 weeks of pregnancy with favourable outcomes. Junichiro et al had used a TH1/TH2 ratio imbalance and a high resistance of uterine radial artery blood flow as a parameter to start IV immunoglobulin in patient of recurrent abortion with a successful outcome but in our case, it was done solely on clinical suspicion.[9]Kim et.al (2022) explored the outcomes of empirical treatment with IVIG combined with Low dose aspirin in women with unexplained recurrent pregnancy loss in a retrospective study involving 93 patients and 113 natural and assisted reproductive technology cycles.

The results were co related with NK cell counts. The live birth rate per cycle was higher in the treatment group regardless of the type of RPL, 75% and 69% in primary and secondary RPL respectively (p value = 0.526).

The results did not differ with regards to the method of pregnancy, the timing of IVIG treatment, the NK cell count or even the presence or absence of autoantibodies. American Society for Reproduction and Embryology do not recommend for routine testing of immune abnormalities in patients of RPL due to low quality of evidence but various data from the literature suggests pre-screening tests like NK cells, TH1/THE2 ration abnormality before starting immunotherapy.[10]Studies have suggested a higher predisposition to congenital anomaly, preterm delivery and fetal growth restriction in women with RPL who took high dose IVIG hence amodified medium dose protocol was employed in our case.[11]We also did not observe any FGR or preterm labour in the case studied. The ratio of miscarriage with abnormal chromosomal karyotype was found to be lower in the IV immunoglobulin group but as such IV immunoglobulin therapy does not increase the chances of chromosomal anamoly.[12]

No side effects were observed on administration of IV Immunoglobulin in our case but Hideto et al observed elevated liver enzymes (18%), headache (8%) , skin rashes (8%),fever (4%) in the IV immunoglobulin group.[6] Our case had a successful outcome with ecosprin and IV immunoglobulin therapy with minimal side effects hence it can be easily said that IV Immunoglobulin therapy has become a research hot spot and hence the importance of reporting of such cases can add significance to the existing literature.

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Figure 1: Keratinisation of Plantar Surface

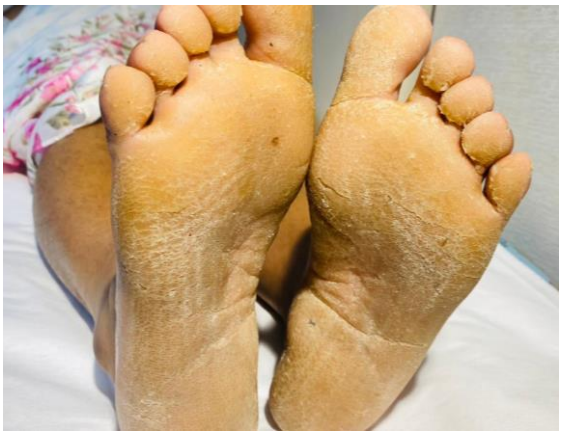
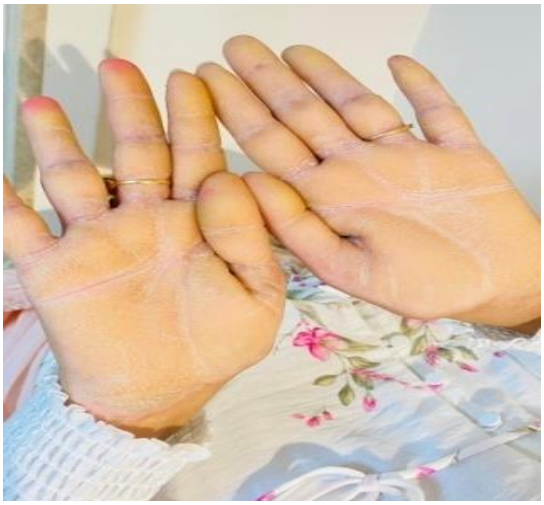


Figure 2: Thick and pale skin on the palms



CONCLUSION

Immunoglobulin therapy is evolving to be effective in idiopathic recurrent abortion. More research is needed in this regard to make them as a recommendation in patients of idiopathic recurrent abortion. More guidelines on pre-screening, timing of administration, dosage schedule has to be studied in detail so as to have a consistent approach in using them in the management of patients of RPL.

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