Intravenous Immunoglobulin (IVIG) in the Prevention of Implantation Failures

G. DE PLACIDO, F. ZULLO,[a,c] A. MOLLO, F. CAPPIELLO, A. NAZZARO, N. COLACURCI, AND G. PALUMBO[b]

Institute of Obstetrics and Gynecology
[b]Department of Biology and Molecular and Cellular Pathology and CEOS/CNR
"Federico II Medical School"
Via Pansini, 5
80131 Naples, Italy
and
[c]Institute of Gynecologic and Pediatric Sciences
Catanzaro Medical School c/o "A. Pugliese" Hospital
Viale Pio X
88100 Cantanzaro, Italy

INTRODUCTION

The recent spread of very sensitive β-hCG assays and assisted reproductive technologies has revealed how high the rate of very early and preclinical abortions is.[1,2] This has made clear that implantation is the true limiting factor of human reproduction. Implantation necessarily implies a specific immunologic interaction between the embryo and the mother: many immune modifications have been claimed in recent literature to explain the tolerance of the fetal allograft.[3,4] This immune approach has given a theoretical basis to different therapeutic strategies for recurrent abortions involving either a partner or donor leukocyte active immunization[5,6] or passive immunization by intravenous immunoglobulins (IVIG)[7] to prevent implantation failures.[8]

This work, based on a previous preliminary investigation,[9] aims to verify the effectiveness of IVIG treatment in the prevention of implantation failures in an open randomized comparative study versus placebo and to identify possible parameters predictive of conditions liable to be successfully treated by this protocol.

MATERIAL AND METHODS

Patients

The patients were thirty-nine women with: a) two or more very early abortions (less than 8 weeks) or biochemical pregnancies (marked by two consecutive increases in β-hCG levels without USG evidence of gestational sac); and b) three or more failed attempts of embryo transfer after IVF, replacing at least three embryos.

[a] Send correspondence to this author.

TABLE 1. Clinical Outcome[a]

	Cases	PR	IR	AR
Group A	18	6/18 (33.3%)	8/45 (17.7%)	1/6 (16.6%)
Group B	21	4/21 (19.1%)	4/61 (6.5%)	2/5 (40.0%)

[a] $p < 0.05$ (Fisher's Exact Test).

Protocol and Study Design

Eighteen patients were randomized in the IVIG treatment group (group A) and 21 in the placebo arm (group B). All patients underwent a superovulation protocol, which included ovarian desensitization by GnRH analogs. Before gonadotropin stimulation, patients received the first administration of 200 ml of immunoglobulin concentrate (20 g, group A) or placebo (group B). A second administration was given when β-hCG was positive and, then, every three weeks up to the 20th week of gestation. Following the treatment all patients were monitored for changes in a) serum profile of immunoglobulins, b) unidirectional "mixed lymphocyte culture" (MFC) (to detect possible blocking factors[5]), and c) trophoblast penetration through a three-dimensional support. The latter test was performed *in vitro* using a specific endometrial primary cell culture, according to a procedure originally described by us, named "double tube microinvasion test" and detailed in Reference 10. In brief, the test consists in matching primary endometrial cell culture (from endometrial biopsies from the previous cycle stimulated in the same way as at the time of implantation), with a choriocarcinoma cell line (JEG-3) in two separate Millipore tubes (5 mm diameter). After 48 hours culture in suspension in Ham F-10 supplemented with 5% FBS to allow cells to adhere to walls and to produce extracellular matrix, the two tubes were put head by head and held together with a cuff. Five days later, a number of trophoblast cells (identified by MoAb PKK1 for cytokeratine) migrated into the endometrium: the entity of this migration and the number of migrated cells was finally measured.

RESULTS AND DISCUSSION

Clinical outcome in group A (IVIG) and B (placebo) is reported in TABLE 1. It may be seen that while the pregnancy rate (PR) was not statistically significant (33.3 vs 19.1), the implantation rate (IR) in the IVIG group was remarkably higher ($p < 0.05$) as compared to the placebo group (17.7% vs 6.5%). The abortion rate (AR) was 16.6% in group A and 40.0% in the placebo group. At T_0 the immunoglobulin serum profile and the one way "mixed lymphocyte culture" (MFC) were not different in patients of both groups; at T1 (*i.e.*, after treatment) "mixed lymphocyte culture" was not significantly modified; the obvious change in the serum immunoglobulin profile was observed in the IVIG group. A good correlation was observed between the "double tube microinvasion test" and the clinical outcome. Only in 3 out of 15 cases tested (4 cases were not assayed because cell cultures were lost), the number of trophoblast cells at 3 mm distance from the interface out of the total number of trophoblast cells at the interface was lower than 5% and, more important, in 2 of these 3 cases an ongoing pregnancy

resulted after IVIG treatment. Among the remaining 12 cases, showing a microinvasion greater than 5% at 3 mm, pregnancy was observed only in a single case. These findings suggest that those cases in which the trophoblast invasion during the test with prepared endometrium is defective may be responsive to an immune treatment.

In view of a possible wide application of the "double tube microinvasion test" as a prognostic assay for the use of the intravenous immunoglobulin in the prevention of implantation failures, and considering the high cost of this treatment, it is clear that more studies, either clinically oriented and/or laboratory based, are necessary.

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@article{Placido1994IntravenousI, title={Intravenous Immunoglobulin (IVIG) in the Prevention of Implantation Failures}, author={G. Placido and F. Zullo and A. Mollo and F. Cappiello and A. Nazzaro and N. Colacurci and G. Palumbo}, journal={Annals of the New York Academy of Sciences}, year={1994}, volume={734} }.Â The recent spread of very sensitive P-hCG assays and assisted reproductive technologies has revealed how high the rate of very early and preclinical abortions This has made clear that implantation is the true limiting factor of human reproduction. Intravenous immunoglobulin (IVIg) is a therapeutic pre-. paration of normal human polyclonal IgG obtained from. plasma pooled from a large number of healthy blood.Â There is a risk of acute renal failure caused by the. deposition of immune complexes formed by exogenous. IgG and the intrinsic IgM rheumatoid factor component.Â dimers in the IVIg pool increases with the number of. donors contributing to the pool. The formation of idiotype Intravenous immunoglobulins (IVIg) are therapeutic preparations of normal human IgG obtained from pools of more than 1000 healthy blood donors and thus contain a wide range of IgG reactivities directed towards external antigens and self-antigens. From: Autoantibodies (Second Edition), 2007.Â In the last decade the use of intravenous immunoglobulin has largely replaced the use of intramuscular immunoglobulin for treatment of immunodeficiency diseases, as the amount of immunoglobulin which can be easily administered is much greater when delivered by the intravenous route. Additionally, studies have shown that patients with primary immunodeficiency disease benefit from the larger doses, and that the serum levels of IgG can be normalized. Embryo Implantation*. Female. Humans. Immunoglobulins, Intravenous / therapeutic use*. Pregnancy. Substances. Immunoglobulins, Intravenous. Intravenous immunoglobulin (IVIG) contains the pooled immunoglobulin G (IgG) immunoglobulins from the plasma of approximately a thousand or more blood donors.Â Immune Thrombocytopenia. A prime use of IVIG is in the treatment of hematological diseases . The first description of the treatment of individuals with ITP with IVIG was by Imbach et al in 1981. [3] They noted that dose administration of IVIG promoted a rapid recovery for children with ITP. Platelet destruction occurs in the spleen.Â Prevention against acute graft versus host disease with IVIG might be mediated by the induction of apoptosis of activated alloreactive CD4 + CD134 + donor T cells. [37]. Other Uses.