

# Intravenous Immunoglobulin (IVIg) for unexplained infertility: a case series

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## Summary

Intravenous Immunoglobulin (IVIg) is a potential treatment for immune mediated reproductive failure (IMRF), but its role in infertility treatments remains controversial. There is evidence that administering IVIg before conception improves pregnancy outcomes. In the present cohort, 13/15 (86%) patients had a live birth after receiving pre-conceptual IVIg at immunomodulatory doses. No serious maternal or fetal side effects directly attributable to IVIg were reported. The present results support the need for a randomized controlled trial (RCT) with this protocol.

**Key words:** Immunology; Infertility; Maternal-fetal medicine.

## Introduction

Intravenous Immunoglobulin (IVIg) has been used for years as an off-label treatment for women with idiopathic recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL). However, studies fail to show a consistent effect of IVIg in such women, presumably because of several issues including study heterogeneity, diverse pathophysiological mechanisms, and lack of biomarkers to diagnose suspected immune mediated reproductive failure (IMRF). There is some anecdotal evidence of its efficacy in certain patients, but correct IVIg dosing, timing of administration and patient selection remains unclear.

## Materials and Methods

Ethics approval was obtained from the McGill University Health Centre Research Ethics Board (MUHC REB, study number 15-408-MUHC). Patients were required to sign an informed consent prior to starting IVIg and were prospectively followed every three months during pregnancy and one month after delivery. Patients 18-42 years old with > 4 unexplained miscarriages, or > 3 unexplained good quality blastocyst transfer failures were referred to the Allergy-Immunology Clinic at the Montreal General Hospital after failing conventional medical treatments. The authors developed a standardized protocol whereby IVIg 600-800 mg/kg was administered 5-10 days prior to embryo transfer (ET) or one month before a planned natural conception as a last resort therapy for these patients. If the patient could not receive IVIg, equivalent doses of subcutaneous immunoglobulin (SCIg) were started one month before planned conception or ET. If successful pregnancy ensued, IVIg was given monthly (or SCIg was given

weekly) until 32-34 weeks of gestation. Patients with contraindications to IVIg or receiving other immunomodulatory treatments were excluded.

## Results

Fifteen patients were included from 08/2014-01/2016; 13 underwent IVF, two conceived naturally with 13/15 (86%) having delivered healthy children, and 2/13 (15.4%) having failed their ET (Tables 1 and 2). No maternal IVIg side effects were reported aside from mild, transient post-infusion headaches in 6/15 (40%) of patients. Two patients developed obstetrical complications. One patient with a history of ulcerative colitis, renal colic, and bilateral hydronephrosis stopped IVIg at 24 weeks because of hospitalization for renal colic. She subsequently developed pyelonephritis, went into pre-term labour (PTL) and delivered a healthy male at 34.5 weeks. Another patient with a history of a 27-week stillbirth and three late second trimester losses (she consented to genetic and pathological analysis for her last loss which was an 18-week sized genetically normal male; there was no evidence of placental insufficiency) developed PTL at 33 5/7 weeks and delivered a healthy male weighing 2,690 grams. There was one IVF twin pregnancy which was delivered vaginally at 37.3 weeks. One fetal anomaly was reported: mild ventriculomegaly was diagnosed at 26 weeks in a genetically normal male. The child had a normal MRI and had no evidence of neurocognitive delay on follow up at 12 months of age. No other adverse fetal events were re-

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Table 1. — *Maternal characteristics before IVIg.*

Total n=15	Primary RIF n=8	Secondary RIF n=2	Primary RPL n=4	Secondary RPL n=1
Mean maternal age	36	40.5	30.75	35
Miscarriages (Mean # per patient)	0.25	0.5	7.5	7
ET failures (Mean # per patient)	5.6	8	0.75	0
Previous successful pregnancies (Mean/patient)	0	1.5	0	1

Table 2. — *Pregnancy outcomes with IVIg.*

Total n=15	Primary RIF n=8	Secondary RIF n=2	Primary RPL n=4	Secondary RPL n=1
Number of pregnancies	6	2	4	1
Number of live births	6	2	5	1
Miscarriages/stillbirths	0	0	0	0
ET failures	2	0	0	0

ported. Interestingly, four patients were successfully treated with SCIg; two patients were treated exclusively with scIg because of IVIg refusal and two other patients elected to continue with scIg after receiving one and two doses respectively of IVIg.

## Discussion

Recently, the Korean Society for Reproductive Immunology Practice Guidelines recommended administering IVIg at 400 mg/kg every 3-4 weeks in early pregnancy only for women with reproductive failure and immune anomalies including elevated NK cells and abnormal Th1/Th2 ratios [1]. The present authors argue two hypothetical points. Firstly, peripheral blood biomarkers might not adequately reflect the local uterine immune status [2]. While some studies have found positive associations between the presence of these biomarkers and IVIg success [3], a cause-effect relationship has not been clearly established. The authors worry that basing a diagnosis on unvalidated laboratory tests might preclude certain women from benefitting from IVIg. Secondly, fetomaternal immune tolerance probably develops before implantation. There is evidence that seminal fluid induces paternal specific T-regulatory cells that are found in uterine draining lymph nodes before conception [4]. Furthermore, cytokine and hormonal signalling provided by the endometrium (and immune cells recruited to the site of implantation) at conception direct trophoblast invasion, spiral artery remodeling, and establish downstream immune mechanisms that maintain fetomaternal tolerance throughout the pregnancy [2]. The present authors therefore propose that to truly impact fetomaternal tolerance, IVIg should be started at immunomodulatory doses before implantation. Indeed, a

meta-analysis of ten controlled studies published in 2013 found that IVIg significantly increased clinical pregnancy rates (1.475 (95%CI: 1.191-1.825)) and live births (1.616 (95%CI: 1.243-2.101)) in women with RIF; 8/10 studies started IVIg before ET [5]. The most recent meta-analysis on IVIg treatment in RPL patients did not find any beneficial effect over placebo but 8/13 studies started IVIg after clinical confirmation of the pregnancy [6]. Upon subgroup analysis, the live birth rate was significantly improved when IVIg was started before conception (RR 1.67 (95% CI 1.30-2.14),  $p < 0.0001$ ) but this was not the case if started after pregnancy diagnosis (RR 1.10 [95% CI 0.93-1.29]).

## Conclusion

Although this is a small cohort, the present IVIg protocol seems to have benefitted a patient population with otherwise dire fertility and pregnancy outcomes. The authors plan to confirm this result with a follow-up RCT. Interestingly, while the present patients were not selected on the basis of allo- or autoimmune anomalies, the authors did observe an 86% live birth rate which is higher than the estimated  $< 30\%$  without treatment. In such patients, who consume excessive private and public healthcare resources to achieve their goals, the present authors believe that a trial of IVIg may be cost-effective; even in the absence of laboratory evidence of IMRF. Of note, while IVIg is safe and well tolerated during pregnancy [6], it is not without risk. Systemic reactions and infusion related side effects can be minimized by substituting IVIg with SCIg which is home-administered. Unfortunately, there are, to the present authors' knowledge, no published studies using SCIg for IMRF. The equivalency of SCIg to IVIg must also be confirmed in larger scale studies.

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