When conventional treatment fails: the role of intravenous immunoglobulin in recurrent pregnancy loss secondary to antiphospholipid syndrome

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Summary: Recurrent pregnancy loss (RPL) is a well-recognized complication of antiphospholipid syndrome (APS). First line therapy consists of low dose aspirin and heparin. Despite conventional therapy some women fail to achieve a successful pregnancy outcome. We describe the case of a patient who had two live births following intravenous immunoglobulin therapy despite previous failure with conventional therapy for RPL in the setting of APS. We will summarize the available literature on intravenous immunoglobulin for this indication.

Keywords: IVIG, antiphospholipid syndrome, recurrent pregnancy loss

INTRODUCTION

The association between antiphospholipid syndrome (APS) and adverse pregnancy outcomes is well recognized with recurrent pregnancy loss (RPL) being the most characteristic feature.¹ In women with primary APS who are untreated, the miscarriage rate has been reported to be as high as 90%.² With appropriate management, more than 70% of pregnant women with APS will deliver a viable live infant.³ The optimal management of APS has not been fully elucidated. This is in part because the mechanisms of pathogenicity of APS in pregnancy are not clear and are likely to be diverse.⁴ Clinical manifestations of obstetric APS are also varied and trials investigating management have shown heterogeneous results.³

We describe a case of successful live birth following intravenous immunoglobulin (IVIG) therapy in a woman who had previously suffered pregnancy loss while receiving low-dose aspirin and low-molecular weight heparin treatment (LMWH).

CASE

A 31-year-old woman was diagnosed with primary APS in 2004 following investigation for two previous first trimester miscarriages. Pathology tests at that time show a positive lupus anticoagulant (LAC), IgG anticardiolipin antibody in a high titre, antinuclear antibody <40 and a negative double stranded DNA. The patient had no features of other autoimmune disease and was otherwise healthy.

The third pregnancy was complicated by HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome at

20 weeks gestation, despite prophylactic aspirin and enoxaparin (40 mg/day) from early pregnancy. Spontaneous intrauterine fetal death followed. Placental histology showed widespread infarction. The patient was continued on aspirin 100 mg/day postdelivery.

The fourth pregnancy ended in miscarriage at 12 weeks gestation, despite enoxaparin 1 mg/kg twice daily and aspirin 100 mg/day. The fifth pregnancy was managed with therapeutic enoxaparin, low dose aspirin and monthly IVIG at 0.4 g/kg/month from eight weeks gestation. This dose of IVIG was chosen following consultation with our Immunologists. It was felt that this was a sufficient dose for immunomodulation and that a higher dose which might provide a more rapid effect was not required.

After initial confirmation of a viable pregnancy on ultrasound at seven weeks, further scans were planned to be performed at 12, 18 and 24 weeks. The patient was reviewed regularly by both the obstetric medicine physicians and obstetricians as well as attending the obstetric review clinic monthly for her infusions. Initial scans showed normal fetal growth and Dopplers; however, a further scan at 34 weeks showed normal growth but small areas of placental infarction. Induction of labour was planned and delivery of a liveborn infant occurred via caesarean section due to a non-reassuring fetal cardiotocograph. The male infant weighed 2410 g and had Apgar scores of 9 and 9 at 1 and five minutes respectively. He was admitted to the special care nursery for prematurity. Placental histology showed focal accelerated villus maturation consistent with impaired uteroplacental perfusion.

Her sixth pregnancy was ectopic. The seventh pregnancy was again managed with monthly IVIG, aspirin and therapeutic dose enoxaparin. She underwent four-weekly fetal scans. The pregnancy was uneventful until 34 weeks at which time the

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Table 1 Published articles reporting use of intravenous immunoglobulin in women with recurrent miscarriage secondary to antiphospholipid syndrome. Ordered by year of publication

Author and year	Number of patients	Study type and treatment	Dose of IVIG	Outcomes
Wapner <i>et al.</i> (1989) ²¹	2	Case report, IVIG + aspirin and heparin after RPL on aspirin/prednisone	1 g/kg/month	Full-term infants
Kajaa <i>et al.</i> (1992) ¹²	3 (4 pregnancies)	Uncontrolled case series, IVIG plus aspirin	1 g/kg/4 weeks	4 live births, 1 preterm
Spinnato <i>et al.</i> (1995) ¹⁰	5	Uncontrolled case series, IVIG plus variable other treatment	Total 2 g/kg/month	5 live-births, 1 preterm at 32 weeks
Valensise <i>et al.</i> (1995) ¹¹	14	Controlled case series (fetal growth compared with control group of uneventful pregnancies), IVIG alone	Total 1 g/kg/4weeks	Normal fetal growth
Marzusch <i>et al.</i> (1996) ⁸	38	Uncontrolled case series, IVIG alone	0.3 g/kg/3weeks	31 live-births delivering at term
Clark <i>et al.</i> (1999) ⁹	15 (19 pregnancies)	Uncontrolled case series, Aspirin, heparin, prednisone and IVIG	Total 2 g/kg/month	16 live-births, reduced pregnancy complications
Branch <i>et al.</i> (2000) ¹⁵	16 (7 IVIG, 9 placebo)	RCT*, IVIG/aspirin/heparin vs placebo aspirin/heparin	Total 2 g/kg/4weeks	Higher rate preterm birth in IVIG group
Diejomaoh <i>et al.</i> (2002) ²⁰	7	Uncontrolled case series, IVIG + aspirin and heparin after >5 RPL on aspirin/heparin	0.5 g/kg/month	Uneventful pregnancies and 7 live-births
Triolo <i>et al.</i> (2003) ¹⁶	40 (21 IVIG, 19 aspirin/LMWH)	Randomised trial, IVIG alone vs aspirin/LMWH	Initial 0.8 g/kg then 0.4g/kg/month	No significant difference between treatment groups
Chang <i>et al.</i> (2006) ²²	1	Case report, IVIG + aspirin and heparin after RPL on aspirin/heparin	1 g/kg/4weeks	2 successful pregnancies (one IUGR [†] , one uncomplicated)
Perricone <i>et al.</i> (2008) ¹³	12 (8 with SLE [‡] alone and 4 with SLE and APLS)	Controlled case series, IVIG vs. aspirin and prednisolone	0.5 g/kg/3weeks	12 live-births in treatment group versus 9 in control group
Dendrinios <i>et al.</i> (2009) ¹⁷	78 (38 IVIG, 40 LMWH/aspirin)	Randomised trial, IVIG alone vs. LMWH/aspirin	0.4 g/kg/4weeks	Higher live-birth rate in LMWH/aspirin group

LMWH, low-molecular weight heparin; APS, antiphospholipid syndrome; IVIG, intravenous immunoglobulin; RPL, recurrent pregnancy loss

*RCT = randomized controlled trial

†IUGR = intrauterine growth restriction

‡SLE = systemic lupus erythematosus

patient was admitted to hospital with hypertension, headache and visual disturbance and went into spontaneous labour. A live-born female infant weighing 2265 g, with Apgar scores of 9 and 9 was delivered via caesarean section and admitted to the special care nursery. Placental histology showed an increase in number of macrophages in the chorion, of uncertain significance and many congested villi but was otherwise normal.

The patient has not had any further pregnancies and remains well.

EVIDENCE FOR USE OF IVIG IN RPL

Initial trials used aspirin and prednisone therapy⁵ to increase the live-birth rate in APS while the subsequent use of combination aspirin and heparin was first described in 1989.⁶ IVIG use in a patient with positive LAC and a history of RPL was reported in 1988.⁷ Since that time there have been a number of further cases of IVIG use in women with RPL secondary to APS^{8–13} (Table 1) with the largest case series describing its successful use in 38 women.⁸

A number of potential mechanisms for the action of IVIG have been postulated over this time, including inhibition of antiphospholipid antibody binding to activated platelets and increased antiphospholipid antibody clearance through binding with the IVIG as demonstrated by a reduction in antibody titres.⁹ The exact mechanism, however, remains largely unknown and is postulated to be multifactorial.¹⁴

A small randomized controlled trial was carried out in 2000¹⁵ comparing IVIG, aspirin and heparin therapy with placebo plus aspirin and heparin, with another randomized trial in 2003¹⁶ comparing IVIG use alone directly to aspirin and heparin

therapy. Both trials showed no statistically significant difference in neonatal and obstetric outcomes between treatment groups. The initial trial did show a trend towards improved neonatal outcomes in the group with adjunctive IVIG usage but was underpowered, including only a total of 16 patients.

A more recent trial comparing IVIG alone to low molecular weight heparin plus low-dose aspirin¹⁷ has shown the heparin/aspirin combination to result in a higher live-birth rate. A Cochrane analysis, using data from the 2000 and 2003 trials, has concluded that IVIG use is associated with increased risk of pregnancy loss or premature birth compared with heparin and low-dose aspirin.¹⁸ The 2000 trial¹⁵ did find a significantly higher rate of preterm delivery in the IVIG group but this rate was due to the elective delivery of two women by caesarean at 35 and 36 weeks due to previous third trimester fetal death. In excluding these two cases, the difference was no longer significant. Triolo *et al.*'s¹⁶ trial in 2003 found no significant difference in preterm deliveries between the two treatment groups. These trials are summarized in Table 1.

While results overall have not supported a role for IVIG as primary or sole therapy, a possible role for its addition in the management of patients with RPL despite treatment with aspirin and heparin has emerged. In a retrospective analysis of their own data, Triolo *et al.* showed that in their patients, IVIG treatment was followed by successful pregnancy outcome in eight of 10 women previously unsuccessfully treated with both heparin and low-dose aspirin.¹⁹

The use of IVIG following failure of conventional therapy for RPL in APS has also been described in a subgroup of seven women who were part of a larger case series²⁰ of 43 women with a history of RPL. These seven women, who had each experienced more than five previous RPL, received monthly

IVIg from 10 to 34 weeks gestation as additional therapy to aspirin and heparin. This combined approach resulted in uneventful pregnancies and term deliveries of healthy infants in all seven women.

Additionally, three case reports have been published reporting the use of IVIg in circumstances similar to the above (Table 1). Wapner *et al.*²¹ described two cases of women that delivered full-term infants after being treated with low-dose aspirin, unfractionated heparin (prophylactic dose) and IVIg. They had previously been managed with aspirin and prednisone and had not been successful in attaining a live birth. Chang *et al.*²² described the case of a single patient who had miscarried while being treated with aspirin and unfractionated heparin. She went on to have two subsequent successful pregnancies while being treated with aspirin, heparin (variable dose ranging from 5000 units twice daily to 15000 units twice daily) and IVIg. While the first pregnancy resulted in delivery of the infant at 32 weeks for the indication of intrauterine growth restriction, the second pregnancy progressed uneventfully to 37 weeks at which time an elective caesarean section was performed. No significant adverse events were reported in either article.

There have been no randomized controlled trials addressing the use of IVIg in refractory cases of APS with RPL. It is also not clear as to whether there are any particular features of these cases which may have aided in decision-making when IVIg was being considered. Part of this may be due to the lack of clear mechanism of action of IVIg. The uncertainty regarding the exact pathogenesis of APS also means that there remain no clear guidelines for treatment of these patients.

Despite this, many experts would agree with the addition of IVIg following failure of conventional therapy. A survey was undertaken in 2008 to determine the practice patterns of experienced physicians in the management of the controversial aspects of antiphospholipid pregnancies.²³ One of the questions asked of the participants was how they would manage the next pregnancy of a patient with late fetal loss despite low-dose aspirin and prophylactic dose LMWH therapy. Twenty percent of responders stated that they would use IVIg with this figure rising to 37% if the patient had failed on therapeutic dose LMWH.

The optimal dose of LMWH has not been assessed with controlled studies.²³ LMWH and unfractionated heparin have been shown to be at least equivalent²⁴ in treatment of APS in pregnancy but studies have used varying doses of LMWH ranging from 20 to 80 mg/day. There are few studies comparing doses of LMWH.²⁵ There are also few studies comparing different regimens of administration of IVIg²⁶ and the optimal method to achieve immunomodulation is not known.²⁷ A wide range of dosing regimens were used in the studies included in Table 1.

DISCUSSION

While the role IVIg played in our patient having two live born infants remains debateable, this case adds to the literature regarding IVIg use as second or further-line therapy in women with APS and RPL.

Therapy with low-dose aspirin and heparin remains the gold standard; however at least 25% of women still fail to achieve a live birth on this therapy,²⁸ demonstrating that these women will continue to search for other therapies.

IVIg is an expensive commodity within Australia. In 2009–2010 approximately \$163.3 million was spent on IVIg²⁹ across all indications equating to approximately \$60 per gram of use. Guidelines set down by the National Blood Authority in Australia³⁰ outline conditions for which IVIg use is currently approved, with RPL associated with APS not listed as an indication. Special permission must therefore be sought from the Red Cross in such cases and justification provided.

Its use is also associated with risks including blood-borne infection, as IVIg is derived from human plasma. While donors are subjected to screening processes, and procedures for virus removal and inactivation are included in the manufacturing process,³¹ the products may still potentially transmit disease. There have been no reports of HIV transmission but there were several outbreaks of hepatitis C associated with IVIg administration in the mid-1990s.²⁷ Other adverse events that have been described include hypersensitivity reactions, acute renal failure and an aseptic meningitis syndrome. Use of IVIg therefore requires careful consideration of risk and benefit in individual cases.

It has now been almost 30 years since the initial case reports were published looking at methods of managing APS in pregnancy. Novel therapies continue to emerge as potential therapeutic approaches³ as more is becoming understood of the pathogenesis of the syndrome. Elements of uncertainty and controversy regarding obstetric APS remain, especially surrounding refractory cases.³² While the use of IVIg is not supported by current evidence, the successful outcome in this patient suggests it may be valuable in certain cases. Further research is required to determine which individuals with RPL and APS may benefit from IVIg.

DECLARATIONS

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Guarantor: JC.

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