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Intravenous Immunoglobulin (IVIG) and Recurrent Spontaneous Pregnancy Loss

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Background

Some cases of unexplained recurrent spontaneous pregnancy loss have been proposed to arise from an undefined immunological barrier to normal placentation. One proposed treatment, active immunization with allogeneic leukocytes, benefits only 8% to 10% of treated couples, who cannot be selected by means of diagnostic testing.(1) Another treatment, passive immunization with intravenous immunoglobulin (IVIG), was promising in uncontrolled trials.(2) IVIG, which is human IgG prepared from pooled plasma, has a diverse antibody profile because thousands of donors contribute to the pool.(3) IVIG treatment has now been evaluated in five randomized controlled trials (RCTs).(4-8) This document addresses the effectiveness of IVIG and the clinical implications of related publications.

Sources

A current literature search located five RCTs which assessed IVIG treatment for recurrent spontaneous pregnancy loss (RSPL). In the studies, eligible couples had at least three,(5-8) or at least two,(4) previous abortions. Two trials were limited to women with primary RSPL (no live births),(5,8) one involved only women with secondary RSPL (at least one live birth),(6) and two trials included both primary and secondary RSPL.(4,7) Required investigations included but were not limited to, hysterosalpingogram and/or hysteroscopy, luteal progesterone and/or endometrial biopsy and karyotype.

Exclusion criteria were IgA deficiency,(5-8) lupus,(6-8) age over 39 years,(5) age over 42 years,(8) and presence of anti-cardiolipin antibody.(4,7,8) All studies described the randomization methods, all made use of a control treatment that could maintain blinding, and all studies provided data on delivery after 28 weeks and newborn status. For this statement success is defined as live birth at or after 28 weeks. IVIG therapy was initiated before conception in two trials,(4-7) and during the first trimester in three trials;(5,6,8) and continued until the first or second trimester.

Methods

The relevant RCTs were examined for estimates of the relative likelihood of live birth in IVIG-treated and control-treated couples. The results for all randomized patients who conceived were included in the meta-analysis. Statistical techniques were used to estimate the average treatment effect with its 95% confidence limits and a heterogeneity statistic.(9)

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Results

The five randomized controlled trials reported on 121 IVIG-treated patients and 125 placebo-treated patients. The aggregate live birth rate was 62% (95% CI 53, 71) in the IVIG group and 54% (95% CI 45, 62) in the placebo-treated controls.

The individual RCT results were as follows.

- In the German multicentre trial, 20/33 IVIG-treated patients and 21/31 albumin-treated patients were successful. IVIG was no more effective than the albumin placebo (relative risk 0.89 95%CI 0.61, 1.35).(5)
- In the American trial, 18/29 IVIG-treated and 11/32 albumin-treated patients were successful. IVIG was 1.66 fold (95%CI 0.93, 2.94) more effective than placebo.(4)
- In the Danish trial among women with secondary RSPL, 9/17 IVIG-treated patients and 5/17 albumin-treated had a live birth after 28 weeks. IVIG was 1.80 fold (95%CI 0.69, 5.13) more effective than placebo.(6)
- In the Canadian trial 12/20 IVIG-treated patients and 10/21 placebo-treated delivered after 28 weeks. IVIG was ineffective in primary RSPL and 1.81 fold (95%CI 0.29, 11.3) more effective than placebo in secondary RSPL.(7)
- In the Italian trial 16/22 IVIG-treated patients and 19/24 placebo-treated delivered after 28 weeks. IVIG was 0.72 fold (95%CI 0.14, 3.56) less effective than placebo.(8)

The results summarized from the five RCTs indicate that IVIG is not effective for primary RSPL (likelihood of live birth 0.98, 95%CI 0.45, 2.13). In secondary RSPL, there was a higher proportion of successful pregnancies with IVIG, but the number of patients was insufficient to rule out a chance finding (2.19, 95%CI 0.65, 7.39).

Adverse effects were not reported frequently in the studies and those observed included transient rash and fever.

Discussion

The effectiveness of IVIG as a treatment for recurrent spontaneous pregnancy loss remains unproven. IVIG does not prevent further losses among women with primary recurrent spontaneous pregnancy loss. A potential effect has been demonstrated in the less prevalent problem of secondary recurrent spontaneous pregnancy loss. The published data are insufficient, however, to exclude the possibility that the treatment also has no value in the latter condition.

Severe side effects of IVIG are rare in well-selected patients. Mild side effects including fever, malaise, myalgia and headache occur in 4% of patients.(3) Severe reactions are encountered in IgA deficient patients; the prevalence of IgA deficiency is 1 per 1000. Nephrotoxicity, alopecia, aseptic meningitis and retinal necrosis are rare but serious side-effects.(3) The potential for harm from immunotherapy during pregnancy cannot be excluded, and potential risk of using a preparation derived from pooled plasma cannot be assessed from currently available data

IVIG treatment is expensive. The cost ranges from \$7000 to \$14000 for a

single course of therapy.

Conclusion

IVIG as a treatment for recurrent pregnancy loss should be evaluated in patients who are informed, consenting participants in an institutional review board approved randomized clinical trial. For the management of recurrent spontaneous pregnancy loss IVIG is an experimental treatment.

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