

June 3, 2010

CIGNA HealthCare
National Appeals Unit
P.O. Box 5225
Scranton, PA 18505-5225

RE: Patient
Provider: Dr. Doctor
Service: IVIg
Date of service: Prior authorization for IVIg (proposed start date 6/11/2010)

Dear Sir or Madam:

I am writing on behalf of Patient to initiate an appeal of CIGNA's denial of coverage of Intravenous Immunoglobulin (IVIg) for treatment of recurrent in vitro fertilization failure (RIF). The appeal form, a release authorizing me to represent Ms. Patient in this appeal, and my HIPAA release are enclosed.

CIGNA's initial denial was based on the fact that RIF is an "experimental" use for IVIg. However, the basis for CIGNA's conclusion is both outdated and not applicable in this case. In addition, there is a large amount of medical literature *supporting* the use of IVIg in this case.

Ms. Patient has undergone two attempts at in vitro fertilization (IVF). Her medical records support Dr. Doctor's clinical judgment that future IVF attempts also will fail unless she is able to be treated with IVIg. For these reasons, we ask that CIGNA reverse its decision and permit Ms. Patient to undergo a trial of IVIg prior to her next attempt at IVF.

I. CIGNA'S BASIS FOR CONSIDERING IVIG TO BE EXPERIMENTAL IS OUTDATED.

CIGNA's 2009 Medical Policy Guideline on Infertility Services states:

CIGNA does not cover ANY of the following infertility services or tests because they are considered experimental, investigational, or unproven: antiprothrombin antibodies, embryotoxicity assay, leukocyte immunization, IV immunoglobulins.

CIGNA Medical Coverage Policy Infertility Services Effective Date 6/15/2009
http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0089_coveragepositioncriteria_infertility_diagnostic_and_treatment_services.pdf
(last accessed 5/20/10) (emphasis added).

CIGNA goes on to explain:

Some authors have suggested that immunological factors may adversely affect fertility. As a result, various testing and treatment modalities have been proposed including, but not limited to, antiprothrombin antibodies, embryotoxicity assay, leukocyte immunization and IV immunoglobulin therapy. Nonetheless, evidence in the published, scientific literature is insufficient to support improved individual outcomes (Royal College of Obstetricians and Gynaecologists [RCOG], 2003).

CIGNA, *supra*.

As noted above, CIGNA bases its policy on IVIg use for RIF on a 2003 RCOG report that concludes “intravenous immunoglobulin (IVIg) does not improve the livebirth rate among those with **unexplained recurrent miscarriage**.” Royal College of Obstetricians and Gynaecologists (RCOG). Scientific Advisory Committee Opinion Paper 5. Immunological Testing and interventions for Reproductive Failure. October 2003. Accessed May 10, 2007 http://www.rcog.org.uk/resources/Public/pdf/SAC_Opinion_Paper_5.pdf (emphasis added).

Unfortunately, only the second edition of the RCOG Opinion Paper is now available on line. However, even the updated paper still claims – erroneously – that “intravenous immunoglobulin (IVIg) does not improve the livebirth rate among those with unexplained recurrent miscarriage.” Royal College of Obstetricians and Gynaecologists (RCOG). “Immunological testing and interventions for reproductive failure (2008) <http://www.rcog.org.uk/womens-health/clinical-guidance/immunological-testing-and-interventions-reproductive-failure> (last accessed 5/27/09). However, this no longer is the state of medical science, even based on the RCOG’s own sources.

The RCOG based its conclusion on selective quotation from an article by Hutton, et al., that concludes that IVIg is not more effective than placebo for the treatment of recurrent miscarriage. Hutton B., et al., “Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review,” *BJOG*. (2007 Feb.);114(2):134-42. However, Hutton also expressly points out that **some studies did find IVIG therapy to be effective, especially when begun prior to pregnancy**.

Two studies observed a statistically significant improvement in the rate of live births with IVIG compared with placebo A meta-analysis of all seven studies produced a non-significant effect favouring [sic] IVIG (OR 1.28, 95% CI 0.78–2.10; P = 0.33). . . . Trials were also stratified according to whether therapy in patients was begun prior to pregnancy or following achievement of pregnancy. . . . In the two studies (n = 102) starting therapy prior to conception, women receiving IVIG had an increased live birth rate (OR 2.39, 95% CI 1.08–5.33; P = 0.03).

Hutton, et al., *supra*. In addition, these results apply to any and all miscarriages, not only to explained, immunologic miscarriage following IVF. Thus, the very source that RCOG relied upon actually supports a contrary result.

CIGNA's current policy is based on an outdated RCOG article. Even the updated article, however, has misleading information based on an over-generalized conclusion. Therefore, CIGNA's policy on IVIg therapy for IVF is at least outdated, if not seriously flawed. More recent articles have shown that IVIg is effective, especially in cases of immunologic IVF failure like Patient's.

II. IVIg IS ESPECIALLY APPROPRIATE IN A CASE LIKE THIS ONE, INVOLVING IVF FAILURE STEMMING FROM IMMUNOLOGIC FACTORS

IVF failure can stem from several causes. In this case, there is a "problem within the uterine environment that does not allow the pregnancy to grow properly. The most frequent environmental causes of pregnancy loss are attributable to immunologic factors followed by thrombophilic or blood clotting factors." Coulam, C. and Hemenway, N., "Immunology may be key to successful pregnancy," *INCIID Insight*. (October 2006) <http://www.inciid.org/article.php?cat=immunology&id=522> (Last accessed 5/24/10) (emphasis added).

"When the mother's immune system cannot or does not respond appropriately to embryonic signals, pregnancy loss can occur." *Ibid*. Several blood tests are used to evaluate the mother's immune system, including NK cells¹, which can be tested with the Reproductive Immunophenotype (RIP) and the NK activation (NKa) assays; T cells, which can be assessed by measuring the activated RIP and regulatory T cells (CD4+25+), and which also has been associated with the presence of Anti-thyroid Antibodies as well as the presence of circulating embryotoxins in the Embryotoxicity Assay (ETA); and B cell function is evaluated by their production of autoantibodies including antiphospholipid antibodies [APA], antinuclear antibodies, antithyroid antibodies and lupus-like anticoagulant. *Ibid*. The testing that has been done in this case demonstrates that immunologic factors are responsible for the repeated pregnancy loss. In such a case IVIg is especially appropriate.

Ms. Patient is a 37 year old woman who has been trying to have a baby for several years. She and her husband came to Doctor's clinic in November 2008 after having tried unsuccessfully to get pregnant for over a year.

¹ Natural Killer cells are a type of immune cells called lymphocytes. CD3-, CD56+, and CD16+ are types of NK cells.

Mr. Patient was tested, and male factor infertility was ruled out. (*See* semen analysis results December 13, 2008 and sperm DNA integrity test results December 15, 2008). Hysterosalpingograms (HSG) determined that Ms. Patient has blocked fallopian tubes. (*See* HSG results Jan. 10, 2009 and Jan. 30, 2009). Dr. Doctor determined, based on these results, that Ms. Patient would not become pregnant by natural means, and IVF was appropriate.

IVF first was attempted in April 2009. Implantation was achieved, but the embryo spontaneously aborted after only two months. IVF again was attempted in December 2009 with similar results. Heparin was used in both attempts at IVF. Intralipid was added for the second attempt. (*See* Doctor's notes). After the second IVF failure, Ms. Patient underwent a battery of immunologic tests. She tested positive for antiphospholipid antibodies (APA) and her natural killer cell (NK) level and cytotoxicity were elevated. (*See* March 2010 Natural Killer cell activity assay (NKa) and reproductive immunophenotype (RIP) and other blood test results).

Natural Killer cell activity or activation assay (NKa) measures the killing activity (cytotoxicity) within each cell. **Increased killing activity is associated with implantation failure and pregnancy loss.** . . . *Ibid.* (emphasis added). Similarly, "many groups have found a strong association between the presence of APA and unsuccessful IVE treatment." Stern, et al., "Antiphospholipid antibodies and coagulation defects in women with implantation failure after IVF and recurrent miscarriage," Vol. 13 No 1, 2006 29-37 *Reproductive BioMedicine Online*.

Thus, there remains no question that the pregnancy loss is due to immunologic factors.

Effective treatment depends on the cause of the pregnancy loss. . . . If [as is the case here,] the cause is related to activated immune cells and their cytokines, treatments include: Intravenous Immunoglobulin (IVIg), Intralipid, and Phosphodiesterase Inhibitors. If either acquired or inherited thrombophilia is causing clotting of the placental vessel and subsequent pregnancy loss, then heparin and aspirin is the treatment of choice. If the blood clotting is the result of an immune process, then steroids and/or IVIg can be used.

Coulam and Hemenway, *supra* (emphasis added). However, in this case, treatment with heparin and intralipid did not work. "Corticosteroid therapy has been shown to be ineffective for [spontaneous abortion] and this treatment is associated with numerous complications during pregnancy, especially preterm delivery." Stricker, R., *et al.*, "Successful treatment of immunologic abortion with low-dose intravenous immunoglobulin." *Fertility and Sterility* 2000;73(3).² The only other possible treatment is phosphodiesterase inhibitors. However, Dr. Doctor feels that the presence of NK cells

² This article addresses all spontaneous abortions, and not just those associated with RIF.

and APA point strongly in favor of IVIg (See Doctor's letter requesting pre-authorization for IVIg). An article by Konova supports his thinking. "Although studies point to a major role of anticoagulation in the treatment of APS [antiphospholipid syndrome] pregnancy, IVIg seems of great importance in women unsuccessfully treated with heparin." Konova, E. "Intravenous Immunoglobulin Therapy in Antiphospholipid Syndrome," *Clinical Reviews in Allergy and Immunology* 2005:29, 229-35. Thus, IVIg therapy is indicated.

For couples with immunological problems such as Mr. and Ms. Patients', the chances of losing a baby increase with each successive pregnancy. "[T]he risk to a third pregnancy after two successive losses nearly triples to 38 %." Coulam, C. and Hemenway, N., *supra*. The next round of IVF would be Mr. and Ms. Patients' third attempt. Their odds without IVIg are slim.

Therefore, IVIg is the best remaining option for this woman, whose chance to carry a child to term is running out. The medical literature supports this use of IVIg as a safe and effective medication for treating immunological IVF failure.

III. IVIg IS AN ACCEPTED THERAPY FOR IMMUNOLOGIC IVF FAILURE

Coulam and Hemenway explain how effective IVIg can be for a patient like Ms. Patient, who has failed IVF repeatedly:

NKa also measures the ability of IVIg to suppress the killing activity. Patients with high NK cell activity that suppress with IVIg in the NKa will respond very well to intravenous immunoglobulin (IVIg) therapy. **In fact, the live birth rate with preconception IVIg is more than 80%, compared to 20% without treatment.**

Coulam and Hemenway, *supra* (emphasis added).

Several other articles also indicate that a trial with IVIg is indicated at this point. Clark, *et al.*, found that "IVIG significantly increase[s] the probability of taking home one or more babies by patients undergoing IVF for infertility and/or early pregnancy loss." Clark, D.A., *et al.*, "Is intravenous immunoglobulin (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF)," *Journal of Assisted Reproduction and Genetics* 2006;23(1). They explain that, "increased numbers and/or activity of circulating blood-type NK-related cells can translate into an unfavorable environment at the fetomaternal interface," and add that "a common theme in patients with IVF failure/infertility and/or recurrent miscarriages has been increased NK activity, increased TH1/Th2 cytokine ratios, and presence of autoantibodies, and patients undergoing IVF have an increased miscarriage rate which . . . appears to be countered by IVIG." Clark, *et al.*, *supra*.

It is by now well established that “[e]levated NKT cells in recurrent pregnancy loss or implantation failure can be ameliorated with IVIG treatment, and result in successful pregnancy.” van den Heuvel, M., et al., “Decline in Number of Elevated Blood CD3⁺ CD56⁺ NKT Cells in Response to Intravenous Immunoglobulin Treatment Correlates with Successful Pregnancy,” *American Journal of Reproductive Immunology* 2007;58(6): 547-547. He reports very convincing results. “Eight of thirty infertile women presented with high numbers of CD56⁺ CD3⁺ NKT cells, which declined after treatment with IVIG. The elevated NKT cell group with or without concomitant autoimmunity achieved a significantly higher successful pregnancy rate over the course of the study, as compared to women with average numbers of NKT cells and no evidence of autoimmunity ($P = 0.018$). Elevated NKT levels alone was an independent predictor of success on treatment ($P = 0.003$.” van den Heuvel, *supra*.

Stricker, *et al.* studied a more specific case and report that “[l]ow-dose IVIG therapy is beneficial for older women with immunologic abortion.” The findings of Stricker’s study also are impressive.

Of the 47 women, 36 received initial IVIG treatment, and 24 subsequently became pregnant. Of these women, 20 continued IVIG treatment through 26–30 weeks of gestation, and 19 (95%) had a successful term pregnancy. Four women discontinued IVIG therapy after 10–12 weeks of gestation, and 3 (75%) had a successful pregnancy outcome. **Of the 11 women who refused IVIG therapy, 7 became pregnant, and all 7 miscarried.** The difference in pregnancy success rate between the IVIG-treated and untreated groups was significant ($P5.001$). Three women had adverse reactions during the low-dose IVIG infusion, and these reactions resolved when the IVIG brand was changed. Fetal abnormalities were not observed.

Stricker, R., *et al.*, “Successful treatment of immunologic abortion with low-dose intravenous immunoglobulin.” *Fertility and Sterility* 2000;73(3) (emphasis added).

Stricker and his colleagues proceed to discuss problems with the design of other studies that did not find such a beneficial effect. Those problems included poor patient selection that deliberately excluded older women and did not adequately screen for immunologic abnormalities. “The resultant comparison between younger women who have a high pregnancy success rate without any treatment significantly biased the outcome of these studies against IVIG therapy. Other problems include irrational or excessive IVIG regimens and inadequate patient screening for immunologic abnormalities.” Stricker, et al., *supra*.

Thus, the medical literature supports the use of IVIg in women with RIF.

IV. CONCLUSION

There is ample medical literature upon which to base the use of IVIg for immunological IVF failure. All alternatives present significant risks that are not present with IVIg. This is an otherwise healthy and active 37 year old woman whose chance at bearing a child is slipping away. Ms. Patient has told Dr. Doctor that she is willing to attempt IVF several more times. However, future attempts are likely to be even less successful without a new intervention. Heparin has been tried and is not helping. Corticosteroid therapy is ineffective and risky. Therefore, the best alternative is IVIg. Without effective treatment, Ms. Patient's medical bills for further IVF attempts will skyrocket far beyond the cost of IVIg. Thus, it is in both CIGNA's interest and Ms. Patient's to try IVIg therapy.

For all of these reasons, we urge you to reverse CIGNA's noncoverage decision and give this woman a chance at the safe and effective treatment that her treating physician deems most appropriate. Of course, if you would like any additional information, please do not hesitate to contact me. Thank you.

Sincerely,

Representative of Patient