

DOI: 10.21767/2476-1974.100001

# Human Chorionic Gonadotropin—Can Nature’s Own Anti-Rejection Agent Help in reducing chronic Rejection in Solid Organ Transplantation?

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## Abstract

The immune changes that accompany pregnancy are in several ways similar to those required for solid organ transplantation. Successful pregnancy involves controlled downregulation of the maternal immune system with increased tolerance of foetal cells expressing paternal HLA antigens. This is mediated principally by human chorionic gonadotrophin which has a documented ability to alter the action of T cells, dendritic cells and natural killer cells as well as increasing vascularisation.

Chronic graft rejection is now the leading cause of graft dysfunction and failure. Long term anti-rejection therapy is accompanied by immune deficiency and an adverse cardiovascular profile. In contrast, overall immune function is preserved in pregnancy and pregnant women generally feel well. As such hCG initially added to conventional therapy may reduce or prevent chronic rejection in transplantation. In the future hCG may even replace long term anti-rejection therapy.

Organ transplantation has no counterpart in nature. The immune system tolerates everything that is ‘self’ and attempts to eliminate everything that does not bear recognizable ‘self’ signatures. Pregnancy represents nature’s best model of solid organ transplantation; a complex graft mismatched at half of all HLA antigens. As such miscarriage is equivalent to graft rejection. In the context of pregnancy, the body has developed several mechanisms of promoting tolerance to paternal tissue antigens not present on the maternal host cells.

These include the immune privilege afforded by the uterus [1] and its peculiar ability to sequester the haplo-nonidentical foetal antigens within the unique envelope provided by the syncytiotrophoblast cells. These express HLA E and G and some HLA C antigens but no HLA A, B or the class II HLA DR DP and DQ antigens [2]. Importantly however, the newly formed trophoblast also secretes human chorionic gonadotrophin (hCG), receptors for which have been reported on several types of immune cells [3,4].

hCG has several actions on the human immune system that promotes tolerance [5,6]. These are summarised in Table 1 and affect many different immune cells. The overall result is an increase in T regulatory cell function with a reduction in Th1 and Th17 type immunity in particular that leads to decreased NK cell activation.

**Keywords:** Human chorionic gonadotropin; organ transplantation; anti-rejection agent

## hCG and Mechanisms of Tolerance

**Table 1:** Summary of the hCG action on the different cells involved in pregnancy

Cell type	Action of hCG	Mechanism	Result of deficient hCG function
Dendritic	Reduced antigen presenting function Reduced DC proliferation Skewing of T cell function to increased Th1 and Th17	Increased indoleamine dioxygenase	Increased anti-pregnancy Th1 and Th17 function and promotion of Tregs

T regulatory	Recruitment to foetomaternal interface Increased IL10 secretion	Decreased local Th17/Th1 type cells that encourage anti-foetal cell activity	Rejection of the early embryo/foetus
NK cell	Reduced activation of peripheral blood cytotoxic NK cells and increased proliferation of cytokine producing uterine NK cells	Reduced killing of foetal cells Coordinated vascularisation of placental bed	Rejection of the early embryo Impaired placentation and raised risk of PET
Extra villous Trophoblast	Increased invasion of maternal spiral arteries Apoptosis of activated T cells	Regulation of fas/fasL expression	Impaired placentation Persistence of harmful activated T cells
Endothelial cells	Increased endothelial proliferation Reduced leucocyte adhesion	Stimulation of vascular endothelial growth factor Reduced E-selectin mediated leucocyte binding	Reduced blood supply to the developing embryo/foetus Increased leucocyte recruitment

## Clinical Experience of hCG in Mechanisms of Solid Organ Graft Autoimmunity and Transplantation Rejection

The importance of hCG in promoting tolerance and reducing the activation of those cells that are involved in rejection was investigated in the 1970s to see if the human hCG could lengthen the survival of skin allografts in mice and rats [7,8]. The absence of any significant benefit may be related to the inactivity of the human hCG to bind to the murine or rat LH/hCG receptors or the development of neutralising immunity to the human protein. More recently hCG was shown to prolong skin allografts in mice [9]. Furthermore, women receiving hCG preconditioning prior to IVF had reduced inflammatory IL17 but increased anti-inflammatory IL27 and IL10 [9]. Interestingly, the improvement in the symptoms of rheumatoid arthritis during pregnancy is due in part to the hCG induced shift of Th1 mediated cellular immunity to a pro-pregnancy Th2 immunity and an increase in T regulatory cell function. These changes are favourable for both pregnancy [10] and for a reduction in pathogenic RA immune activity [11]. Therapeutically, hCG has been used successfully in the management of paraneoplastic neuropathy mediated by anti-Hu antibodies [12].

### Safety of hCG

For the vast majority of women pregnancy is not associated with any significant susceptibility to infective illness or with any significant ill health. Indeed some women even feel better when pregnant. In the context of hCG, women with minimally aggressive gestational trophoblastic neoplasia and with hCG levels exceeding 3000mIU/ml remain otherwise in good health [13]. This supports the notion that hCG by itself is virtually free of any significant side effects and is both subtle and specific in its action. This contrasts with the numerous side effects of currently used anti-rejection therapy that includes corticosteroids, ciclosporin, tacrolimus azathioprine, mycophenolate mofetil and a range of T cell specific antibodies. Used in combination these therapies are both very expensive and have a profound ability to suppress many aspects of human immune function. This leaves the transplant recipient open to range of infections and in the long term certain malignancies. Better tolerated, more specific and cheaper alternatives are clearly required.

Most cases of graft loss are now due to technical factors and chronic rejection mediated by T cells [14], B cells [15] and, NK cells [16]. Acute and subacute graft rejection mediated by preformed allo-antibodies and complement activation is now a rare event owing to careful assessment for preformed panel reactive antibodies [17] and class I and sometimes class II cross matching. Chronic graft rejection involving direct and indirect allo-recognition [14] remains a significant cause of impaired graft function. With its safety and lack of overt immune suppression, regular hCG may be valuable in reducing the possibility of chronic graft rejection. This often involves low level immune activation and vascular damage. In most instances the latter is mediated by host immune cells that recognise non-self HLA class I and II antigens on the transplanted organ. Once started this process becomes more difficult to switch off. As hCG may encourage endothelial proliferation there is also the intriguing possibility that any vasculopathy may partially offset by new vessel formation. Nonetheless, a variety of immune suppressive agents are used early and sometimes prophylactically to down regulate the host immune system so that it does not easily become activated by any foreign HLA proteins on the transplanted tissues. Anti-rejection therapy often involves increasing these drugs and using additional agents. The latter include anti-thymocyte globulin and some of the newer humanised monoclonal antibodies that have a more global or more potent suppressive action on the immune system. There is a careful balance between adequate suppression of the immune system to prevent rejection and excessive suppression that leaves the patient open to infection with microbes of low pathogenicity.

### Using hCG in Reducing Allograft Rejection

Normal pregnancy can teach us a great deal about immune mechanisms of allo-recognition and how these may be attenuated to reduced or even prevent graft rejection. To test the ability of hCG to reduce the immune reactivity between host and transplanted cells would be relatively straight forward. In the laboratory, hCG may be added in increasing concentrations to donor and recipient peripheral blood mononuclear cells in a mixed lymphocyte reaction to see if suppression was evident.

Any favourable changes may then encourage the addition of hCG to conventional anti-rejection therapy. The principal outcome measures would be the proportion of patients retaining clinically acceptable graft function and frequency of use of anti-rejection therapy. Secondary outcome measures may include precise measures of graft function as well as immune based assessments of cell activation and basal and stimulated cytokine production. hCG treatment used as an adjunct to conventional anti-rejection therapy should not carry any additional risks or side effects. The therapy should be avoided in patients with any suggestion of a malignancy owing to its ability to promote angiogenesis even though this has only so far been demonstrated for endometrial vessels [18]. It should initially be used at doses that lead to levels of circulating hCG comparable to those evident in a mid-trimester pregnancy. If this is tolerated without any problem then higher doses may be tried. While hCG is presently given as a subcutaneous injection, the best method and frequency of hCG administration in transplantation needs to be determined. The initial trials should be undertaken in women and aimed at comparing graft survival and function when hCG is added to conventional therapy. Ideally the use of hCG should recapitulate the gradually increased maternal exposure to the paternal HLA proteins seen in pregnancy. As this is difficult in solid organ transplantation, the next best option is that the therapy is started a few days ahead of any planned organ transplantation so as to positively modulate the host immune system before it is exposed to any mis-matched donor HLA proteins. In the first instance the therapy should be tested in patients undergoing kidney transplantation as rescue therapy with dialysis is routinely available. In time and with positive results, liver and heart transplants could also benefit from this therapy which may then be extended to males. In the long term there is even the possibility of using this therapy in bone marrow transplantation.

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