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INTERPRETATION OF ACTIVATED NK CELLS & NK CYTOTOXICITY IN WOMEN WITH FAILED IVF OR EARLY RECURRENT MISCARRIAGE

INTRODUCTION

Natural Killer Cells (NK Cells) are a subset of lymphocytes that have the ability to target and kill malignantly transformed or virally infected cells. They express receptors with limited diversity. These are capable of recognising damaged cells or tissue that is antigenically foreign such as a foetus or graft. It is with this latter point in mind that NK Cells are now considered important in embryo rejection in women with early recurrent miscarriage and recurrent failed IVF. In the past the absolute NK Cell count was considered predictive of reproductive outcome. However, there is now much evidence to suggest that it is the activated NK Cell population that is of most importance. Activated NK Cells express the CD69 cell surface marker. Thus, assessing the absolute numbers of CD69 positive CD16/CD56 positive lymphocytes by flow cytometry provides an accurate assessment of activated NK Cells.

ACTIVATED NK CELLS

The reports issued by the Reproductive Immunology Centre give both an absolute value for the number of circulating NK Cells as well as a percentage. If the value of total CD69 positive NK Cells exceeds 1.0 x 106/L then this has been associated with a relatively reduced reproductive outcome. In our experience, women with a CD69 NK Cell value greater than1.0 x 106/L have approximately one third the rate of successful pregnancy to term, compared to those with a level less than 1.0 x 106/L. Clearly, this field is changing rapidly and we will continue to modify the actual level of NK Cells predictive of reproductive outcome based on our continuing research.

NK CYTOTOXICITY & SUPPRESSION USING PREDNISOLONE, IVIg & INTRALIPID

Therapeutically, prednisolone, Intralipid and intravenous immunoglobulin (IVIg) therapy has been used to improve outcome in women with recurrent failed IVF and recurrent early miscarriage. These therapies are formally assessed by determining the ability of these agents to suppress the killing of target cells by the patient's NK cells. The results are expressed as the percentage reduction in killing at effector:target ratios of 12.5:1, 1:25 and 1:50 in the presence of different physiological concentrations of prednisolone and IVIg. Thus if the baseline killing is 7% and at the same effector:target ratio IVIg at 12.5mg/ml suppresses the killing to 1% this is an 86% reduction.

The therapy that produces the greatest reduction in NK cell killing would be most appropriate to use. In general, however, a reduction of NK cytotoxicity to below 20% is desirable for improved IVF outcome. Our results thus far have not shown an additive effect of prednisolone and IVIg and therefore at present we suggest one or other therapy is used.

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