

Commonly used preventive therapy for recurrent miscarriage proved ineffective in large trial

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An immune response to pregnancy (in which the uterus rejects the embryo or foetus) is said to explain a large number of otherwise "unexplained" miscarriages. Thus, preventive treatment designed to suppress this immunological rejection during implantation and pregnancy has become a commonly accepted—albeit innovative—approach to preventing recurrent pregnancy loss. A range of "immunomodulatory" treatments are offered, most of which are non-evidence based and the latest of which is a drug known as recombinant human granulocyte-colony stimulating factor (rhG-CSF), a regulator of neutrophils and other lymphocytes activating and protecting the immune system. This is widely used (and licensed) in cancer medicine to increase white blood cells after chemotherapy.

Now, a large randomised placebo-controlled study—the largest of its kind, the RESPONSE trial—described here today at the 34th Annual Meeting of ESHRE has found no evidence that rhG-CSF given in the first trimester of [pregnancy](#) improves outcomes in women with a history of unexplained recurrent pregnancy losses. The results are presented by honorary research fellow Dr. Abey Eapen from Tommy's National Centre for Miscarriage Research at the University of Birmingham, UK, and the University of Iowa Hospital and Clinics, USA. The study, a controlled randomised trial involving 150 women with a history of unexplained miscarriage, was performed at 21 hospitals in the UK.

As background to the study Eapen said that evidence in favour of rhG-CSF in the prevention of recurrent pregnancy loss was based on just one single-centre randomised trial and four further observational studies, which all suggested a statistically significant increase in pregnancy and live birth rates in the [treatment](#) groups.

In this study, with an endpoint defined as clinical pregnancy rate at 20 weeks gestation, 76 women were randomised to rhG-CSF and 74 to placebo. All subjects had had at least three unexplained miscarriages, were aged between 18 and 37 years, and were trying to conceive naturally.

At follow-up, results showed a clinical pregnancy rate at 20 weeks of 59.2% in the rhG-CSF group, and of 64.9% in the placebo group, suggesting a neutral effect of the treatment. With further follow-up, these rates were similarly evident in live birth.

"Worldwide, granulocyte-colony stimulating factor is widely used in reproductive medicine to treat pregnancies conceived both naturally and after assisted reproduction following recurrent miscarriages," said Eapen. "Some studies have suggested statistically significant improvements in clinical pregnancy rates, but we here have high quality evidence that rhG-CSF is not an effective treatment for patients with unexplained recurrent miscarriages."

Miscarriage—whether recurrent or not—is a common and distressing complication of pregnancy, especially in IVF when so much emotion and effort has been invested in treatment. Estimates are that around 1-2% of all couples experience [recurrent pregnancy loss](#), but Eapen said that it is difficult to estimate the actual numbers using rhG-CSF. "It's a relatively new treatment and is offered mainly through private miscarriage and IVF clinics."

He also described reproductive immunology is a "relatively new and young" branch of reproductive medicine. "We first need to agree on an acceptable definition based on reliable and reproducible laboratory investigations before labelling a miscarriages as immune mediated," he said. "Most of immunotherapy medications tested so far through high quality trials have been shown to offer no benefit. Women diagnosed with recurrent [miscarriages](#) are vulnerable, so it's important that, if they're given immune modulatory treatment for [recurrent miscarriages](#), they are counselled about success rates and potential risk/benefits, even in a research setting, let alone routine clinical practice."

Even after a diagnosis of recurrent miscarriage, the majority of pregnancies do have a favorable outcome. "But," said Eapen, "it is still very important that these women are investigated and managed in a specialist miscarriage clinic for counselling, support, evidence-based investigation, and an opportunity to take part in research. Healthy diet and management of modifiable risk factors may also help."

More information: Abstract O-064, Tuesday 3 July 2018 - Recombinant Human Granulocyte - Colony Stimulating Factor (rhG-CSF) in women with unexplained recurrent pregnancy losses (RESPONSE Study): randomised, double-blind, multicentre, placebo controlled trial

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