IMMUNOTHERAPY IS INAPPROPRIATE FOR TREATMENT OF RECURRENT PREGNANCY LOSS!

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Recurrent miscarriage (RM) defined as three or more consecutive miscarriages affects 0.5-1% of all women. In a minority, parental chromosome abnormalities, uterine malformations or endocrine and thrombophilic disturbances may be risk factors. In many cases immunological risk factors can be identified in peripheral blood but these might not per se cause RM. However, since a) several studies of the immune interactions at the feto-maternal interface and genetic-epidemiologic studies document an immunological background for many RM cases and b) immunological disease is often caused by immune reactions exclusively localised in the target organ, a demand for the detection of immunological disturbances in peripheral blood is not necessary to suggest an immunological etiology. If other causes are excluded in a particular case it may be assumed that the etiology is mainly immunological and most trials of immunotherapy in RM have accordingly included patients due to the absence of non-immunological risk factors.

Three kinds of immunotherapy have been tested in placebo-controlled trials (PCTs): prednisone, immunization with lymphocytes from the partner or third party donors (LIT) and intravenous (i.v.) immunoglobulin (IvIg). The latter two will be discussed here.

Leukocyte immunization therapy (LIT): The PCTs of LIT have provided conflicting results. A Cochrane meta-analysis of relevant trials (1) concluded that paternal and third party LIT provide no significant beneficial effect over placebo in preventing miscarriages. The odds ratios (OR) for life birth after the two treatments compared with placebo were 1.23 and 1.39, respectively (not significantly elevated). If all trials of LIT were included in a single meta-analysis the OR for birth after LIT becomes 1.34 (95% CI 0.83-2.15), which is close to significance. In the Cochrane analysis separate analysis in patients with primary RM was not carried out, although LIT was found efficient in a previous meta-analysis of outcome in primary RM patients from 8 PCTs (2). Furthermore, in a meta-regression analysis undertaken in this study, the effect of LIT increased with the number of previous miscarriages, indicating that this is an effect modifier of importance in meta-analyses of LIT in RM. This may be due to the fact that the prevalence of immunological risk factors increases with the number of previous miscarriages: e.g. particular HLA-DR alleles and mannann-binding lectin deficiency.

There was statistically significant heterogeneity between the outcomes in the trials of partner LIT in the Cochrane analysis (1) questioning the rationale of calculating a pooled OR. Furthermore, the analysis did not distinguish between different immunizing doses and routes of administration although the immunizing procedures in the included trials differ substantially (3). In vaccination: very low and high doses normally induce tolerance whereas intermediate doses induce immunization which (in pregnancy) may harm the fetus. In the trials in the Cochrane analysis, one administered <100 x 10^6 and another >1500 x 10^6 cells to all patients. Intradermal/subcutaneous injections are prone to induce immunization whereas i.v. administration normally induces tolerance. In one LIT trial all cells were given intradermally whereas in other trials all cells were given i.v. Furthermore, in one trial cells for injection were stored overnight whereas in other trials cells were injected within a few hours after being drawn from the partner/donor. Storage of lymphocytes may alter their immunogenetic properties radically, which may impair the anti-abortive effect.

Intravenous immunoglobulin (IvIg): IvIg for preventing RM has so far been tested in seven PCTs with very different results. In the Cochrane meta-analysis, the pooled OR for live birth was 0.98 (95% CI 0.61-1.58) and it was concluded that there was no benefit of IvIg in the treatment of RM. However, as pointed out previously (4) the trials were very different with regard to the frequency of patients who a) had four or more miscarriages (19-100%), b) had secondary RM (0-79%) or c) had autoantibodies (0-43%). Furthermore, there was an extreme diversity with regard to the starting time of infusions ranging from before conception to gestational week 9, the number of infusions and the amount of IvIg/placebo given at each infusion (20-75g). The patient populations included in the PCTs and the treatment protocols were thus extremely heterogeneous and the information obtained by the combination of these trials in a meta-analysis is limited. Knowledge about patient subsets and treatment modalities being associated with the largest treatment effect is necessary for the optimal design of future PCTs of IvIg treatment.

In a meta-analysis distinguishing between primary and secondary RM (4), the OR for live birth in IvIg-treated secondary RM patients was 1.60 (95% CI 0.70-3.66; p = 0.27). The apparent
benefit of IVlg in secondary RM (statistically significant in our own two IVlg trials) is consistent with epidemiological and immunological findings suggesting that secondary RM comprises an entity where immunological risk factors dominate. The IVlg doses used in autoimmune disorders are empirical. Frequently used regimens are: 0.4g/kg body weight daily for 5 consecutive days or 1g/kg body weight/day for two days at four weeks intervals. The doses used in most RM trials have generally been much smaller and only in our two trials have doses approaching the aforementioned doses been used. The starting time of IVlg infusions is crucial since obviously any therapy for RM should start before the embryo is dying or already dead. Since it takes weeks to obtain the full immunomodulating effect of IVlg it is therefore important to start infusions from gestational week 5 or before if a beneficial effect is to be obtained. In spite of this, in three trials infusions were only started in week 6-8 after the detection of fetal heart action. Pregnancies being viable at this gestational age display a good spontaneous prognosis, the success rate after allocation to placebo treatment will be high and it will be difficult to detect any therapeutic effect of IVlg.

Risks of immunotherapy: The risks of LIT have been heavily exaggerated by its opponents — however, a large study reported a very low frequency of side effects of the treatment (5). Considerable achievements have been reached in the reduction of the possible risk of transmission of infections agents by IVlg by donor screening and virus inactivation procedures and there has not been reported any transmission of pathogens after IVlg since the early 1990s.
Conclusions: The current Cochrane meta-analysis (1) of immunotherapy in RM combines studies that are too heterogenous for combination. However, if a meta-analysis suggests that LIT with donor or partner cells may increase life birth rate by 34%. Instead of completely rejecting the efficacy of immunotherapy, the Cochrane review should conclude that some types of immunotherapy in RM look very promising but more PCTs are needed. New PCTs of LIT should take into account lessons learned from the previous PCTs and meta-regressions. New meta-analyses of LIT should, as a minimum, look into effects according to doses of the immunization agent, the route of administration, the number of miscarriages and according to whether the patients had suffered primary or secondary RM.

New prospective PCTs of IvIg focusing on patients with secondary RM and using an infusion protocol associated with a high success rate in this subgroup as described by our group (3,4) should be also be conducted. Unfortunately, the pharmaceutical companies seem to be reluctant to support further PCTs of IvIg in RM because of the negative conclusion from the current Cochrane meta-analysis. It would be disastrous for the RM patients if research in this promising treatment is being stopped prematurely.

References