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Abstract title:

Precision diagnostics of endometrial immune dysregulation significantly improves clinical success rates in assisted reproduction treatments.

Study question:

Does endometrial immune dysregulation have an impact on the clinical outcomes of assisted reproduction treatments (ART) in persistent ART failure or other ART contexts?

Summary answer:

Endometrial immune dysregulation is detected across the full ART patient population, and its accurate identification leads to increased embryo implantation and clinical pregnancy rates.

What is known already:

Endometrial immune cells are crucial for embryo implantation, tissue remodelling and vascularisation during early pregnancy and maternal-embryo tolerance. Alterations in the endometrial immune environment have been described in ART patients with recurrent treatment failure, leading to the proposal of immunomodulatory therapies as a potential treatment strategy. However, current approaches for the identification of immune imbalances are usually based on the analysis of peripheral immune markers, which do not accurately reflect the endometrial environment, or on the assessment of a limited number of local immune parameters. This incomplete characterization of the endometrial immune landscape complicates the selection of effective personalized interventions.

Study design, size, duration:

This is a multi-centre retrospective cohort study analysing the endometrial immune cell content of 3628 patients undergoing own-oocyte cycles or oocyte/embryo donation cycles with/without PGT-A between January 2022 and August 2025. Endometrial immune dysregulation (pro-inflammatory, anti-inflammatory or mixed profiles) was identified and targeted therapy proposed when indicated. Prevalence of imbalanced profiles in relation to the patient's clinical history, and the influence of the endometrial immune profile on clinical outcomes were evaluated.

Participants/materials, setting, methods:

NK, T (Th1, Th2, Th17, Treg) and B-cells were quantified using flow cytometry in endometrial biopsies obtained during the window of implantation (ImMap® test, iGLS, Spain). Patients were classified as immunologically balanced or imbalanced based on cell counts. Prevalence of imbalanced profiles was assessed among patients with repetitive implantation failure, or

recurrent miscarriage. A subset of 521 patients was followed to embryo transfer, and implantation (+) and clinical pregnancy rates (CPr) were compared between groups.

Main results and the role of chance:

Endometrial immune profiling revealed that 25.25% of patients presented alterations in at least one of the parameters analysed. Within this group, most patients showed a pro-inflammatory profile (63.1%), followed by anti-inflammatory (23.58%) and mixed profiles (13.32%). Prevalence of immunological imbalance was comparable between patients with and without recurrent implantation failure and recurrent miscarriage, suggesting that endometrial immune dysregulation is not restricted to these conditions.

Regarding clinical outcomes, immunologically imbalanced patients undergoing PGT-A achieved significantly improved results compared to balanced patients in the embryo transfer performed immediately after immune assessment and targeted-therapy recommendation (+: 53.5% vs 38.1%, *p*=0.048; CPr: 49.3% vs 30.9%, *p*=0.016, 2). These findings suggest that the underlying cause of infertility was accurately identified and support the value of endometrial immune assessment beyond persistent ART failure.

Finally, outcome stratification according to embryo allogenicity associated the transfer of semiallogenic euploid embryos (own-egg cycles) after an imbalanced diagnosis with significantly improved outcomes compared to balanced patients (+: 59.5% vs 34%, *p*=0.016; CPr: 54.8% vs 27.7%, *p*=0.009, 2). In contrast, no significant improvement was observed after the transfer of fully allogenic embryos (egg/embryo donation cycles) (+: 44.8% vs 42%; CPr: 41.4% vs 34%), suggesting that these cases require specific immune adaptation mechanisms.

Limitations, reasons for caution:

This is a retrospective study. Any clinical benefits of endometrial immune assessment and/or modulation need to be confirmed by randomised-controlled trials or interventional studies. Also, immune cell accumulation or depletion do not necessarily reflect functional activation or deactivation, which should be confirmed using complementary analyses.

Wider implications of the findings:

Endometrial immune dysregulation may underlie infertility in a substantial proportion of ART patients, not limited to those with persistent failure. Accurate identification of patients with immune alterations, and the specific immune dysregulation involved, is essential for the development of effective personalised treatments.

Study funding/competing interest(s):

No external funding was obtained for this study.

The authors have nothing to declare.

Trial registration number:

N/A

Keywords

Endometrial immune system; Immune dysregulation; Immunotherapy; Precision diagnostics.