UTIMPRO Endometrial Immune Profiling: Advancing Precision Care in Assisted Reproductive Treatment

I. Clinical Care Context

In vitro fertilization (IVF) has revolutionized the treatment of infertility, offering hope to millions of couples worldwide. However, despite significant technological advancements, success rates remain relatively low, with Repeated Implantation Failure (RIF) and Recurrent Pregnancy Loss (RPL) being particularly challenging scenarios.[1]

The endometrium plays a crucial role in embryo implantation and early pregnancy maintenance. Mounting evidence suggests that immune dysregulation in the uterine environment may contribute to implantation failure and pregnancy loss. Endometrial Immune Profiling (EIP) was developed by MatriceLab Innove to identify immune imbalances and guide personalized treatment strategies to optimize endometrial receptivity and improve IVF outcomes.

II. Background of Endometrial Immune Profiling

Endometrial Immune Profiling using MatriceLab's UTIMPRO test involves the detailed analysis of immune cells and biomarkers within the endometrium during the implantation window. This approach provides critical insights into the local immune environment and its impact on fertility outcomes.

Key aspects of EIP include:

- Assessment of the immunoregulated balance between Th1 / Th2 cytokine expression
- Quantification and state of maturation of uterine natural killer (uNK) cells
- Evaluation of implantation-related factors

The UTIMPRO method employs RT-qPCR to quantify the expression of key immune markers:

- IL-18/TWEAK mRNA ratio: Indicates local angiogenesis and potential Th1 deviation
- CD56+ cell count: Reflects uNK cell mobilization
- IL-15/Fn-14 mRNA ratio: Indicates uNK cell maturation and cytotoxic activation

Based on these markers, endometrial immune profiles can be classified into four types:

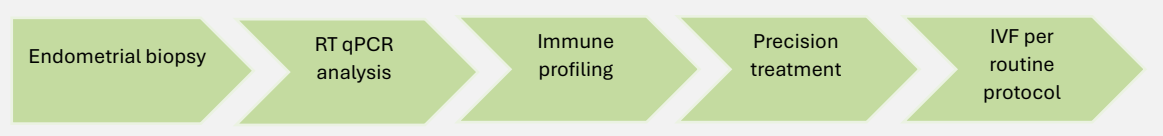
- Balanced activation (normal)
- Under-activation
- Over-activation
- Mixed profile

While these four profiles represent distinct immune states, there is a biological relationship between over-activated and mixed profiles, as both involve heightened immune activity in the endometrium. The mixed profile, however, can be understood as a state of immune over-activation where the body is attempting, but failing, to regulate the immune response through the suppression of NK cell maturation.

Test procedure

The foundation of EIP is an endometrial biopsy, which is collected during the mid-luteal phase in a short outpatient procedure using a Cornier Pipelle. The sample is stored in a small test

container and mailed to MatriceLab for analysis. Within a few days, a report with the individual endometrial immune profile is sent to the clinic and personalized precision treatment is initiated for the patient by the IVF physician.



Prevalence of Immune Dysregulation

A key finding from clinical studies is the high prevalence of immune dysregulation among infertile women. Studies have shown consistently that 75-80% of patients with unexplained Repeated Implantation Failures or unexplained Recurrent Miscarriages exhibit uterine immune imbalances that may impede the embryo implantation process.[2]

Importantly, this high prevalence of immune dysregulation is not limited to patients with a history of repeated failures. A recent randomized controlled trial revealed that even in a cohort of patients with relatively good prognosis, 78% exhibited immune imbalances in the endometrium at the presumed time of implantation. This finding suggests that endometrial immune dysfunction may be a more widespread phenomenon in infertility than previously recognized, potentially affecting outcomes even in patients without a history of repeated failures.

III. Precision Treatment Concept

Principles of precision treatment

The core principle of EIP is to guide personalized treatment strategies based on a patient's specific immune profile. This precision medicine approach aims to address underlying immune imbalances that may be impeding successful implantation and pregnancy.

Treatment recommendations are tailored individually to the identified immune profile:

Under-activated profile	• Endometrial scratching to promote uNK cell maturation • hCG supplementation to stimulate uNK proliferation and angiogenesis • Exposure to seminal plasma (intercourse after embryo transfer)
Over-activated profile	• Glucocorticoids to reduce Th1 cytokines and NK cell cytotoxicity • Higher dose progesterone support • Intralipid infusion or low molecular weight heparin for patients resistant to glucocorticoids
Mixed profile	• Individual combination of treatments for under- and over-activation

By addressing the specific immune imbalance present, EIP-guided treatments aim to create a more receptive endometrial environment for embryo implantation and development.

Safety & tolerability

EIP testing and associated precision treatments have demonstrated a favorable safety and tolerability profile, suggesting a low-risk approach to potentially improving IVF outcomes:

- EIP Testing: The endometrial biopsy required for EIP is a routine, minimally invasive outpatient procedure, with a positive safety profile. The risk of complications such as infection or significant bleeding is low.

- Precision Treatments: The treatments used in EIP-guided protocols are generally well-tolerated:
    - Glucocorticoids: Commonly used at low doses and for a limited duration, significant side effects are rarely reported.
    - Intralipid infusions: Generally considered safe, with no serious adverse events reported in the context of EIP-guided treatment.
    - Low molecular weight heparin: Commonly used at low doses and for a limited duration, significant side effects are rarely reported.
    - hCG supplementation: Well-tolerated when used judiciously, and when precautions are taken to avoid ovarian hyperstimulation syndrome.
    - Endometrial scratching: A minimally invasive procedure with a generally positive safety profile.
- Safety: While long-term follow-up data are still being collected, no increased risk of adverse pregnancy outcomes has been observed in pregnancies resulting from EIP-guided treatments. [3, 4]

IV. Clinical validation

The validation of Endometrial Immune Profiling (EIP) as a diagnostic tool and its potential to guide personalized treatment in IVF has been the focus of recent research. Implementation of EIP-guided personalized treatment has demonstrated promising results in improving IVF outcomes:

- Increased live birth rates, especially for patients with previous implantation failures and sub-optimal embryo quality,
- Potential to reduce time to pregnancy and number of IVF cycles required,
- Avoidance of unnecessary add-on treatments,
- Opportunity for natural conception in some cases,
- No reported significant side effects or adverse events related to EIP-guided treatments,
- Improved patient counselling and management of expectations based on individual immune profiles.

EIP testing and precision treatment have been the subject of rigorous clinical studies in patients undergoing Assisted Reproductive Treatment. A pivotal clinical trial demonstrated the benefits of the EIP approach in challenging cases of Repeated Implantation Failure. The study compared 193 patients who received EIP-guided precision treatment to a matched control group of 193 patients receiving standard care.[3]

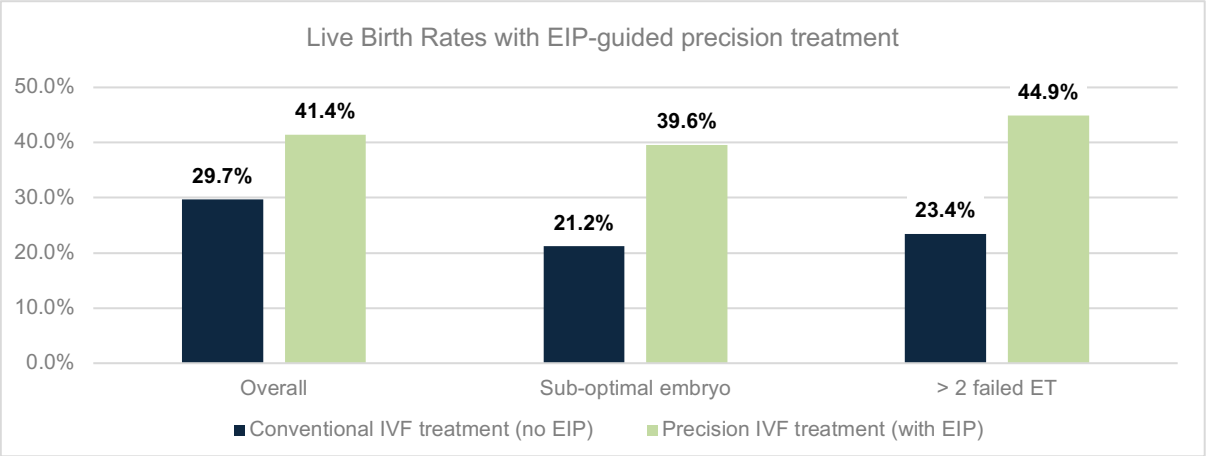
Key findings matched-cohort study:

- Significantly higher live birth rate in the EIP group compared to the control group (30.5% vs. 16.6%, OR: 2.2 [1.27-3.83], *p*=.004)
- Drastically reduced rate of miscarriage per initiated pregnancy in the EIP group (17.9% vs. 43.2%, OR: 0.29 [0.12-0.71], *p*=.005)
- Patients presenting without dysregulation (22%) did not differ from their matched controls in terms of live birth rate and miscarriages.

A recent randomized controlled trial confirmed the efficacy of EIP-guided precision treatment in improving IVF outcomes.[4] The study further validated EIP-guided precision treatment, and included 378 patients undergoing IVF, with 78% showing immune dysregulation.

Key findings randomized controlled trial:

- Significant increase of live birth rate (LBR) from 29.7% with conventional care to 41.4% with EIP-guided personalized treatment (OR: 1.75 [1.04-2.92], *p*=.030)
- Larger benefits observed in patients with sub-optimal embryo quality (LBR: 21.2% vs. 39.6%, OR: 2.43 [1.28-4.61]) and in patients with a history of ≥2 failed embryo transfers (LBR: 23.4% vs. 44.9%, OR: 2.66 [1.26-5.63]).
- EIP-guided personalized treatment shows a number needed to treat (NNT) of 9 patients, with even lower numbers in subgroups like women with suboptimal embryos or previous implantation failures, where only 6-7 patients need treatment to achieve one additional live birth.



V. Conclusion

Endometrial Immune Profiling using MatriceLab's UTIMPRO test represents a significant advancement in the field of reproductive medicine, offering a path to more personalized and more successful IVF treatments. The high prevalence of immune dysregulation underscores the potential importance of this approach in improving overall IVF success rates.

By identifying and addressing immune imbalances in the endometrium, EIP has the potential to improve outcomes for a wide range of patients undergoing IVF, not just those with a history of previous failures. The favorable safety profile and tolerability of both the testing procedure and precision treatments add to the appeal of this approach.

As science continues to unravel the complex interplay between the immune system and reproduction, EIP stands at the forefront of precision medicine in IVF, offering new hope to patients struggling with infertility by enabling physicians to optimize outcomes with assisted reproductive treatment.

References

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