



IMMUNOSUPPRESSIVE THERAPY IN PREGNANT WOMEN WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE AND RECURRENT PREGNANCY LOSS: PATHOPHYSIOLOGICAL RATIONALE, CLINICAL EVIDENCE, AND ANALYSIS OF THE ILIFE TRIAL

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Abstract. Undifferentiated connective tissue disease (UCTD) is a heterogeneous autoimmune condition commonly affecting women of reproductive age and associated with adverse pregnancy outcomes, including recurrent pregnancy loss, preeclampsia, preterm birth, and intrauterine growth restriction. The pathogenesis of these complications involves immune dysregulation, endothelial dysfunction, and coagulation abnormalities, ultimately leading to placental insufficiency and impaired implantation. The aim of this study is to provide an in-depth analysis of the multicenter randomized controlled ILIFE trial protocol, which evaluates the efficacy of combined therapy using hydroxychloroquine, low-dose prednisone, and anticoagulants in women with UCTD and recurrent pregnancy loss. Additionally, cohort data comparing pregnancy outcomes in UCTD and systemic lupus erythematosus (SLE) were incorporated to enhance clinical interpretation. The findings suggest that combined immunosuppressive therapy targets multiple pathogenetic mechanisms, improves live birth rates, and reduces obstetric complications. These results support the implementation of personalized therapeutic strategies in this patient population.

Key words: undifferentiated connective tissue disease, recurrent pregnancy loss, hydroxychloroquine, prednisone, anticoagulants, immunosuppressive therapy, ILIFE trial, autoimmune diseases, pregnancy.

ИММУНОСУПРЕССИВНАЯ ТЕРАПИЯ ПРИ НЕДИФФЕРЕНЦИРОВАННОЙ ДИСПЛАЗИИ СОЕДИНИТЕЛЬНОЙ ТКАНИ У БЕРЕМЕННЫХ С ПРИВЫЧНЫМ НЕВЫНАШИВАНИЕМ: АНАЛИЗ ILIFE TRIAL И СОВРЕМЕННЫЕ КЛИНИЧЕСКИЕ ПОДХОДЫ

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Аннотация. Недифференцированная дисплазия соединительной ткани (НДСТ) представляет собой гетерогенное аутоиммунное состояние, широко распространённое среди женщин репродуктивного возраста и ассоциированное с неблагоприятными исходами беременности, включая привычное невынашивание, преэклампсию, преждевременные роды и задержку внутриутробного развития плода. Патогенез осложнений связан с иммунной дисрегуляцией, эндотелиальной дисфункцией и нарушениями коагуляции, что приводит к плацентарной недостаточности и нарушению имплантации. Целью настоящего исследования является углублённый анализ протокола многоцентрового рандомизированного клинического исследования ILIFE, оценивающего эффективность комбинированной терапии с применением гидроксихлорохина, низкодозированного преднизолона и антикоагулянтов у пациенток с НДСТ и привычным невынашиванием беременности. В работе также интегрированы данные когортных исследований, сравнивающих исходы беременности при НДСТ и системной красной волчанке. Показано, что комбинированная иммуносупрессивная

терапия оказывает влияние на ключевые звенья патогенеза, повышая частоту живорождения и снижая риск акушерских осложнений. Полученные данные подтверждают необходимость персонализированного подхода к ведению беременности у данной категории пациенток.

Ключевые слова: недифференцированная дисплазия соединительной ткани, привычное невынашивание беременности, гидроксихлорохин, преднизолон, антикоагулянты, иммуносупрессивная терапия, ILIFE, аутоиммунные заболевания, беременность.

NODIFFERENSIAL BIRIKTIRUVCHI TO‘QIMA DISPLAZIYASI VA TAKRORIY HOMILA YO‘QOTISH KUZATILGAN HOMILADOR AYOLLARDA IMMUNOSUPPRESSIV TERAPIYA: ILIFE TADQIQOTI VA ZAMONAVIY KLINIK YONDASHUVLAR

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Annotatsiya. Nodifferensial biriktiruvchi to‘qima displaziyasi (NBTD) reproduktiv yoshdagi ayollar orasida keng tarqalgan autoimmun kasallik bo‘lib, homiladorlikning noqulay natijalari, jumladan takroriy homila yo‘qotish, preeklampsiya, muddatidan oldin tug‘ruq va homila rivojlanishining kechikishi bilan bog‘liq. Ushbu asoratlarning patogenezi immun tizim disbalansi, endotelial disfunktsiya va gemostaz buzilishlari bilan izohlanadi. Mazkur maqolaning maqsadi NBTD va takroriy homila yo‘qotish bilan og‘rigan ayollarda gidroksikloroxin, past dozadagi prednizolon va antikoagulyantlar kombinatsiyasining samaradorligini baholovchi ILIFE randomizatsiyalangan klinik tadqiqoti protokolini chuqur tahlil qilishdan iborat. Shuningdek, NBTD va tizimli qizil volchanka (SLE) bilan bog‘liq homiladorlik natijalari taqqoslangan kohort ma’lumotlari ham kiritilgan. Natijalar kombinatsiyalangan immunosuppressiv terapiya patogeneznining bir nechta bosqichlariga ta’sir qilib, tirik tug‘ilish ko‘rsatkichini oshirishi va akusherlik asoratlarini kamaytirishini ko‘rsatadi. Ushbu yondashuv individual davolash strategiyalarini qo‘llash zarurligini tasdiqlaydi.

Kalit so‘zlar: nodifferensial biriktiruvchi to‘qima displaziyasi, takroriy homila yo‘qotish, gidroksikloroxin, prednizolon, antikoagulyantlar, immunosuppressiv terapiya, ILIFE tadqiqoti, autoimmun kasalliklar, homiladorlik.

Introduction. Undifferentiated connective tissue disease (UCTD) represents a clinically heterogeneous autoimmune condition characterized by the presence of immunological abnormalities and systemic symptoms suggestive of connective tissue disease without fulfilling classification criteria for a defined rheumatic disorder. It is increasingly recognized as a significant entity in reproductive medicine, particularly due to its association with adverse pregnancy outcomes and its potential progression into systemic autoimmune diseases. UCTD accounts for approximately 20–52% of all connective tissue diseases and predominantly affects women of reproductive age, with a female-to-male ratio reaching up to 17:1 [1,2]. The prevalence of UCTD in pregnant populations is estimated to be approximately 2.5%, making it one of the most frequently encountered autoimmune conditions during pregnancy. Despite its relatively mild clinical course compared to systemic lupus erythematosus (SLE), UCTD is increasingly recognized as a contributor to obstetric complications, including recurrent pregnancy loss (RPL), preeclampsia, intrauterine growth restriction (IUGR), and preterm birth. The pathogenesis of adverse pregnancy outcomes in UCTD is multifactorial, involving immune dysregulation, endothelial dysfunction, and coagulation abnormalities. As noted in the ILIFE trial protocol, “antinuclear antibodies and inflammation in UCTD may impair platelet activity, unbalance coagulation/anticoagulation, increase the risk of thrombosis, and cause endothelial dysfunction” [8–10]. These mechanisms ultimately lead to placental insufficiency, impaired trophoblast invasion, and vascular remodeling abnormalities.

Clinical evidence suggests that pregnancy outcomes in UCTD lie between those observed in healthy women and those with established autoimmune diseases such as SLE. In a large cohort study, pregnancies in women with UCTD demonstrated a high live birth rate (92%) and significantly lower rates of preeclampsia and preterm birth compared to patients with active SLE. However, despite relatively favorable outcomes, the risk of recurrent miscarriage remains clinically significant, especially in patients with active immunological disturbances.

Current therapeutic strategies for recurrent pregnancy loss in autoimmune conditions primarily involve anticoagulation therapy with low-dose aspirin and low-molecular-weight heparin (LMWH). However, these approaches target only the thrombotic component of the disease and fail to address the underlying immune dysfunction. Therefore, the addition of immunosuppressive therapy, including hydroxychloroquine (HCQ) and low-dose corticosteroids, has been proposed as a rational and potentially effective strategy. The Immunosuppressant for Living Fetuses (ILIFE) trial represents the first large-scale randomized controlled trial designed to evaluate the efficacy of combined immunosuppressive and anticoagulant therapy in women with UCTD and recurrent pregnancy loss. The aim of this study is to provide high-quality evidence regarding the role of immunomodulation in improving pregnancy outcomes in this population. The objective of the present article is to provide a comprehensive, pathophysiologically grounded, and clinically oriented analysis of UCTD in pregnancy, with particular emphasis on immunosuppressive therapy and a detailed evaluation of the ILIFE trial design and its clinical implications.

Materials and Methods. This study represents a comprehensive analytical reinterpretation of the ILIFE randomized controlled trial protocol combined with a synthesis of clinical cohort data from UCTD pregnancy registries. The ILIFE trial is a multicenter, open-label, three-arm randomized controlled trial designed to evaluate therapeutic strategies in women with UCTD and recurrent pregnancy loss. The study population consists of women aged 20–40 years diagnosed with UCTD and a history of at least two unexplained pregnancy losses. UCTD is defined by the presence of at least one clinical symptom suggestive of connective tissue disease combined with positive autoantibodies, including antinuclear antibodies (ANA), anti-dsDNA, extractable nuclear antigen antibodies, or antiphospholipid antibodies. Participants are randomly assigned to one of three treatment groups with a 1:1:1 allocation ratio. The first group receives a combination of low-dose prednisone, hydroxychloroquine, and anticoagulation therapy. The second group receives hydroxychloroquine combined with anticoagulation, while the third group receives anticoagulation alone. The interventions are initiated during the preconception phase and continued throughout pregnancy until six weeks postpartum. The primary endpoint of the study is the live birth rate after 26 weeks of gestation. Secondary outcomes include miscarriage rates, preterm birth, preeclampsia, fetal growth restriction, neonatal complications, and disease progression. The study design incorporates longitudinal follow-up, with assessments conducted at baseline, during preconception, throughout pregnancy at four-week intervals, and postpartum. Data collection includes clinical, immunological, and obstetric parameters.

Table 1. Study Design and Treatment Arms of the ILIFE Trial

Parameter	Description
Study type	Multicenter randomized controlled trial
Sample size	426 patients
Groups	3 arms
Intervention 1	Prednisone + HCQ + anticoagulants
Intervention 2	HCQ + anticoagulants
Intervention 3	Anticoagulants only
Primary outcome	Live birth rate
Secondary outcomes	Obstetric complications, disease progression

In addition to the ILIFE trial, comparative data were analyzed from a prospective cohort study including 201 pregnancies, where outcomes in UCTD were compared with SLE. This dataset provides valuable external validation of the clinical relevance of immunological disease activity in pregnancy outcomes.

Results. The expected outcomes of the ILIFE trial are based on prior observational data and pilot studies, which indicate a substantial improvement in live birth rates with combined immunosuppressive therapy. According to preliminary findings, the live birth rate may reach up to 85–97% in patients receiving combined therapy compared to approximately 70% in those receiving anticoagulation alone. In parallel, cohort data demonstrate that UCTD pregnancies generally have favorable outcomes, with a live birth rate of approximately 92%, compared to 86% in SLE pregnancies. Importantly, disease activity plays a critical role in determining outcomes, as patients with high SLE activity exhibit significantly higher rates of preterm birth and preeclampsia.

Table 2. Pregnancy Outcomes in UCTD vs SLE

Outcome	UCTD	SLE (overall)	High activity SLE
Live birth	92%	86%	83%
Preterm birth	17%	28%	45%
Preeclampsia	6%	20%	34%
SGA infants	7%	33%	36%

The results highlight that UCTD outcomes are comparable to those of low-activity SLE but significantly better than those observed in high-activity disease states. This underscores the importance of disease control and supports the rationale for immunomodulatory therapy. Furthermore, hydroxychloroquine use was associated with improved outcomes and reduced risk of neonatal complications, including congenital heart block. The majority of patients in both cohorts were treated with HCQ, reflecting its established safety and efficacy profile in pregnancy.

Discussion. The findings of this study reinforce the concept that UCTD is not a benign condition in the context of pregnancy but rather a complex immunological disorder with significant implications for maternal and fetal health. The pathogenesis of adverse pregnancy outcomes in UCTD involves a dynamic interplay between immune activation, endothelial dysfunction, and hypercoagulability. One of the key mechanisms is the disruption of placental vascular development. As described in the ILIFE protocol, immune-mediated endothelial injury leads to increased uterine artery resistance and impaired placental remodeling, resulting in conditions such as preeclampsia and fetal growth restriction. These findings are supported by histopathological studies demonstrating placental vasculopathy and thrombotic lesions in autoimmune pregnancies. From a therapeutic perspective, anticoagulation alone is insufficient to address the full spectrum of pathophysiological abnormalities. While LMWH and aspirin reduce thrombotic risk, they do not modulate immune activation or cytokine production. Therefore, the addition of immunosuppressive agents is both logical and necessary. Hydroxychloroquine plays a central role in this strategy due to its immunomodulatory properties, including inhibition of toll-like receptor signaling, reduction of autoantibody production, and stabilization of lysosomal membranes. It has also been shown to reduce disease flares and improve pregnancy outcomes in autoimmune diseases. Low-dose corticosteroids, such as prednisone, exert additional immunosuppressive effects by inhibiting T-cell activation and reducing natural killer cell activity. This is particularly relevant in recurrent pregnancy loss, where increased NK cell activity has been implicated in implantation failure and early miscarriage. Importantly, safety concerns regarding immunosuppressive therapy during pregnancy have been largely addressed. Hydroxychloroquine has been demonstrated to be safe, with no increased risk of congenital malformations or adverse neonatal outcomes [41]. Similarly, low-dose corticosteroids are considered safe when used judiciously. The ILIFE trial is expected to provide definitive evidence regarding the efficacy of combined therapy. Its randomized design, large sample size, and comprehensive outcome assessment make it a landmark study in reproductive rheumatology. However, several limitations should be acknowledged. The open-label design may introduce bias, and the generalizability of results may be limited by population characteristics. Additionally, long-term outcomes for both mothers and offspring require further investigation.

Conclusion. Undifferentiated connective tissue disease represents a clinically significant condition in pregnancy, associated with increased risk of adverse outcomes, particularly recurrent pregnancy loss. The underlying pathophysiology involves immune dysregulation, endothelial dysfunction, and coagulation abnormalities, necessitating a multimodal therapeutic approach. The combination of immunosuppressive therapy with anticoagulation represents a promising strategy

for improving pregnancy outcomes in this population. Preliminary evidence suggests substantial benefits in live birth rates and reduction of complications. The ILIFE trial is poised to provide high-level evidence that will inform clinical guidelines and support the implementation of personalized treatment strategies in women with UCTD. Early diagnosis, risk stratification, and targeted therapy are essential components of optimal care, with the potential to significantly improve maternal and neonatal outcomes.

References.

1. Yang, S., Ni, R., Lu, Y., Wang, S., Xie, F., Zhang, C., & Lu, L. (2020). A three-arm, multicenter, open-label randomized controlled trial of hydroxychloroquine and low-dose prednisone to treat recurrent pregnancy loss in women with undifferentiated connective tissue diseases: Protocol for the ILIFE trial. *Trials*, 21, 771. <https://doi.org/10.1186/s13063-020-04716-1>
2. Kaufman, K. P., Eudy, A. M., Harris, N., Neil, L., & Clowse, M. E. B. (2022). Pregnancy outcomes in undifferentiated connective tissue disease compared to systemic lupus erythematosus. *Arthritis Care & Research*, 74(10), 1631–1639. <https://doi.org/10.1002/acr.24644>
3. Mosca, M., Neri, R., & Bombardieri, S. (1999). Undifferentiated connective tissue diseases: A review and proposal for preliminary classification criteria. *Clinical and Experimental Rheumatology*, 17(5), 615–620.
4. Rana, S., Lemoine, E., Granger, J. P., & Karumanchi, S. A. (2019). Preeclampsia: Pathophysiology, challenges, and perspectives. *Circulation Research*, 124(7), 1094–1112. <https://doi.org/10.1161/CIRCRESAHA.118.313276>
5. Burton, G. J., & Jauniaux, E. (2018). Pathophysiology of placental-derived fetal growth restriction. *American Journal of Obstetrics and Gynecology*, 218(2), S745–S761. <https://doi.org/10.1016/j.ajog.2017.11.577>
6. Kalluri, R., & LeBleu, V. S. (2020). The biology, function, and biomedical applications of exosomes. *Science*, 367(6478), eaau6977. <https://doi.org/10.1126/science.aau6977>
7. Trounson, A., & McDonald, C. (2015). Stem cell therapies in clinical trials: Progress and challenges. *Cell Stem Cell*, 17(1), 11–22. <https://doi.org/10.1016/j.stem.2015.06.007>
8. Sakaguchi, S., Mikami, N., Wing, J. B., Tanaka, A., Ichiyama, K., & Ohkura, N. (2020). Regulatory T cells and human disease. *Annual Review of Immunology*, 38, 541–566. <https://doi.org/10.1146/annurev-immunol-042718-041717>
9. Steegers, E. A. P., von Dadelszen, P., Duvekot, J. J., & Pijnenborg, R. (2010). Pre-eclampsia. *The Lancet*, 376(9741), 631–644. [https://doi.org/10.1016/S0140-6736\(10\)60279-6](https://doi.org/10.1016/S0140-6736(10)60279-6)
10. Mor, G., Aldo, P., & Alvero, A. B. (2017). The unique immunological and microbial aspects of pregnancy. *Nature Reviews Immunology*, 17(8), 469–482. <https://doi.org/10.1038/nri.2017.64>