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Optimization of Pregnancy Management in the Context of Undifferentiated Connective Tissue Dysplasia: A Literature Review

Yunusova Zarnigor Maksadovna

Samarkand State Medical University, Uzbekistan

Abstract Undifferentiated connective tissue disease (UCTD) is a diagnosis applied when clinical and serological findings do not fully meet established criteria for specific rheumatic diseases but indicate underlying autoimmunity. UCTD occurs more frequently in women, particularly of reproductive age, and has a significant impact on pregnancy. Studies demonstrate that affected patients face higher risks of spontaneous abortion, preeclampsia, intrauterine growth restriction, and preterm birth. However, with proper disease control, preconception counseling, and adequate medical care, favorable pregnancy outcomes can be achieved. Screening for Anti-Ro/SSA, Anti-La/SSB, aPL, and other antibodies before conception is essential, as they are associated with obstetric complications. Management strategies must be individualized: nonsteroidal anti-inflammatory drugs, corticosteroids, hydroxychloroquine, and azathioprine are considered relatively safe, while methotrexate, leflunomide, and mycophenolate mofetil are strictly contraindicated. Pregnancy in UCTD patients requires a multidisciplinary approach involving obstetricians and rheumatologists, with intensified monitoring including ultrasound and Doppler assessments. Overall, further research into the complex interplay between UCTD and pregnancy, as well as the development of clear clinical guidelines, remains a pressing need.

Keywords Undifferentiated connective tissue disease, Pregnancy, Autoimmune diseases, Preeclampsia, Preterm birth, Immunosuppressive therapy, Hydroxychloroquine

1. Introduction

Undifferentiated connective tissue diseases (UCTD) are more common in women than in men, particularly during reproductive age [1,2]. The relationship between autoimmune disease and reproduction is bidirectional: the disease can affect a woman's reproductive health, while pregnancy can alter the course of the disease [2]. Historically, women with autoimmune diseases were advised against childbearing due to the risk of disease exacerbation and adverse perinatal outcomes. However, the impact of pregnancy on disease course and the influence of autoimmune diseases on pregnancy outcomes vary depending on the type of disease [4]. It is well established that women with connective tissue diseases (CTD) have an increased risk of pregnancy complications such as spontaneous abortion, preeclampsia (PE), fetal growth restriction, and preterm birth (PTB) [3,5]. Nevertheless, with adequate preconception counseling, good disease control, and appropriate medical care, a safe and complication-free pregnancy is achievable [1,4]. The most common CTDs include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), systemic sclerosis (SSc), and inflammatory myopathies [6]. Each disease has defined diagnostic criteria. However, when clinical and serological features do not fully meet these criteria, the diagnosis of undifferentiated connective tissue disease (UCTD) is made [2,6]. Thus, UCTD encompasses conditions characterized by laboratory evidence of autoimmunity and symptoms seen in other CTDs [7]. The effect of pregnancy on UCTD course and the influence of UCTD on pregnancy outcomes remain insufficiently studied, and clear clinical guidelines are lacking [7]. Therefore, the aim of this study was to review available literature on pregnancy course, maternal and fetal outcomes, and therapeutic approaches in women with UCTD.

Definitions. Pre-pregnancy flare was defined as the worsening of pre-existing CTD-related symptoms or the appearance of new ones. Hypertension was diagnosed when systolic blood pressure exceeded 140 mmHg and/or diastolic blood pressure exceeded 90 mmHg on at least two consecutive measurements during pregnancy [8]. Preeclampsia was defined as new-onset hypertension with or without proteinuria developing after 20 weeks of gestation in previously normotensive women. Eclampsia was characterized by

* Corresponding author:
sammi-xirurgiya@yandex.com (Yunusova Zarnigor Maksadovna)
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generalized tonic-clonic seizures during pregnancy, in the context of hypertensive disorders, not attributable to other causes [9]. Pregnancy loss included spontaneous abortion, therapeutic abortion, intrauterine fetal demise, and neonatal death [10]. Preterm birth was defined as delivery before 37 weeks of gestation. Ectopic pregnancy referred to implantation of the embryo outside the uterine cavity. Postpartum hemorrhage was defined as excessive uterine bleeding after delivery [10,11]. Premature rupture of membranes (PROM) before 37 weeks was also considered a high-risk complication.

Placental abnormalities included placenta previa, placental abruption, placenta accreta, and placental infarction [12,13].

Counseling before, during, and after pregnancy. Pregnancy in women with UCTD carries higher maternal and fetal risks compared with healthy women [14,15]. Therefore, whenever possible, these patients should be referred to high-risk pregnancy centers for preconception counseling and specialized care during gestation. Maternal and fetal outcomes are better when conception occurs during quiescent disease [16,17]. Thus, controlling disease activity before pregnancy is critical. Preconception evaluation should include assessment of disease activity and major organ involvement. Women with UCTD should receive detailed counseling on their individual risk profiles, and maternal-fetal risks should be openly discussed. Treatment regimens must be adjusted by discontinuing teratogenic drugs and continuing medications compatible with pregnancy [18,19,20].

Testing for Anti-Ro/SSA, Anti-La/SSB, antiphospholipid antibodies (aPL), and Anti-dsDNA antibodies is recommended before conception, as these are associated with pregnancy complications [21,22]. Anti-TPO and Anti-TG antibodies should also be screened, since they are common in UCTD and linked to fetal growth restriction, congenital heart block, and other adverse outcomes [23,24].

Additionally, a history of adverse obstetric outcomes (such as PE, stillbirth, spontaneous abortion) should be considered when planning closer monitoring and prophylactic treatment, such as low-dose aspirin [25,26].

Management. A multidisciplinary and individualized approach involving obstetricians and rheumatologists is essential in managing pregnant women with UCTD. Early and active UCTD represents a major risk factor for poor reproductive outcomes; therefore, intensified maternal and fetal monitoring is required [27]. The optimal monitoring schedule is still unclear, but women with risk factors should undergo more frequent evaluations. Rheumatologic assessments are recommended every 4–8 weeks, and obstetric evaluations monthly. Fetal ultrasound and Doppler monitoring should be guided by antibody positivity and disease severity. Fetal echocardiography is specifically recommended for Anti-Ro/SSA–positive women [28].

Since pregnancy and the postpartum period may accelerate disease flare or progression to a defined CTD [29,30], women with UCTD should promptly report new symptoms to their physicians. Postpartum treatment regimens should also be reviewed, taking into account the safety of medications during breastfeeding [31].

Disease management and prevention of pregnancy complications: What is the treatment of choice during pregnancy?

The most frequently used medications in pregnancy, with an acceptable safety profile, include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and antimalarial drugs. In more severe cases—particularly when internal organs are affected or there is insufficient response to other therapies—immunosuppressive agents are required [32,33].

Immunotherapy may also help prevent placental insufficiency by regulating immune system and vascular function. Thus, immunosuppressive drugs not only relieve symptoms and prevent relapse and progression of the disease but may also reduce pregnancy complications [34]. However, the efficacy of therapy in pregnant women with UCTD has been poorly studied. Methotrexate (MTX), leflunomide, and mycophenolate mofetil (MMF) are strictly contraindicated during pregnancy and must be discontinued before conception: at least 6 weeks for MMF and at least 3 months for MTX [35].

Nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are not associated with congenital malformations and are not contraindicated during the first and second trimesters. However, except for low-dose aspirin, their use is not recommended in the third trimester because they increase the risk of premature closure of the ductus arteriosus. There is insufficient evidence regarding the safety of selective COX-2 inhibitors in pregnancy; therefore, they should be avoided [36,37]. Aspirin, a salicylate NSAID, has anti-inflammatory, analgesic, antipyretic, and antithrombotic effects. During pregnancy, it may be used not only for rheumatic diseases and other inflammatory conditions but also for the treatment of antiphospholipid syndrome and prevention of preeclampsia (PE). Low-dose salicylates are compatible with breastfeeding, but high-dose aspirin is not recommended [38].

Corticosteroids. Corticosteroids are considered safe throughout all trimesters of pregnancy. Non-fluorinated glucocorticoids (e.g., prednisone and prednisolone) cross the placenta only in small amounts. For example, after a 20 mg prednisone dose, only about 10% reaches fetal plasma. Therefore, low doses of prednisone and prednisolone are considered safe for use in pregnant women with rheumatic disease [39]. Fluorinated glucocorticoids (e.g., dexamethasone and betamethasone) cross the placental barrier and may be used for promoting fetal lung maturation.

However, corticosteroids during pregnancy may increase certain risks:

- premature rupture of membranes,
- maternal complications such as gestational hypertension, gestational diabetes (GDM), osteoporosis, and infection [40].

Initial evidence suggested that corticosteroid use during the first trimester may increase the risk of cleft palate in the fetus by 3.4-fold (Park-Wyllie et al., 2000). However, a large Danish cohort study (51,973 pregnancies) did not confirm this association [41].

Therefore, the lowest effective dose required to control maternal disease should be used during pregnancy. High doses should be reserved only for life-threatening organ involvement.

Breastfeeding. Glucocorticoids are generally considered safe during lactation, as only minimal amounts are excreted in breast milk. However, when taking prednisone at doses ≥20 mg, it is recommended to discard breast milk for 4 hours after intake, since peak drug concentrations in milk occur around 2 hours post-dose [43].

Antimalarial Therapy. Hydroxychloroquine (HCQ) can be used in patients diagnosed with SLE as well as in pregnant women with UCTD.

- HCQ reduces clinical disease activity,
- improves pregnancy outcomes,
- decreases the risk of thrombosis in the presence of antiphospholipid antibodies,
- reduces the risk of congenital heart block (CHB) in the fetus [44].

Fetal Safety

HCQ crosses the placenta; however, extensive clinical observations have shown that it:

- is not teratogenic,
- does not increase the risk of congenital malformations,
- does not cause growth retardation or delays in intellectual development.

Therefore, HCQ should not be discontinued during pregnancy; on the contrary, it is recommended to continue treatment even before conception.

Immunosuppressive Drugs

Azathioprine (AZA)

- Azathioprine is the most commonly used immunosuppressive drug during pregnancy in DBTD, SLE, and other autoimmune diseases.
- It is considered safe in pregnancy because the placenta metabolizes it in such a way that active metabolites are not formed and thus barely cross into the fetus.
- Dosage: maximum of 2 mg/kg per day (higher doses should be avoided).
- Studies have shown that AZA does not increase the risk of congenital malformations during pregnancy and contributes to positive pregnancy outcomes.

Anticoagulant and Antiplatelet Therapy

Antiphospholipid Antibodies (aPL) and UCTD

- Antiphospholipid antibodies (aPL) are frequently present in pregnant women with DBTD.
- The presence of aPL is associated with pregnancy complications such as:
  - o recurrent pregnancy loss (RPL),
  - o intrauterine growth restriction (IUGR),
  - o preeclampsia (PE),
  - o preterm birth.

2. Conclusions

Undifferentiated connective tissue dysplasia (UCTD) during pregnancy poses a significant risk to both maternal and fetal health. Spontaneous miscarriages, preeclampsia, intrauterine growth restriction, and preterm birth frequently occur in the context of this disease. Nevertheless, through careful pregnancy planning, controlling the disease prior to conception, regular monitoring, and individualized management, many complications can be prevented.

Successful pregnancy outcomes in women with UCTD require a multidisciplinary approach, involving close cooperation between obstetricians, gynecologists, rheumatologists, and other specialists. Moreover, appropriate drug selection and the use of safe dosages ensure favorable results for both mother and child.

A review of the literature shows that clear clinical guidelines for managing UCTD during pregnancy have not yet been sufficiently developed. Therefore, conducting large-scale clinical studies and creating unified protocols for physicians remain urgent needs.

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