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PREGNANCY OUTCOME IN PATIENTS WITH CONNECTIVE TISSUE DISEASE (CTD) IN A TERTIARY CARE HOSPITAL

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Abstract

Background: *Connective tissue diseases (CTDs) are autoimmune disorders that primarily affect women of reproductive age. Their impact on pregnancy outcomes remains a significant concern, especially in low-resource settings where data is scarce.*

Objective:*This study aimed to evaluate maternal and fetal outcomes in pregnant women diagnosed with CTDs at a tertiary care hospital.*

Methods: *A prospective observational study was conducted at Jinnah Postgraduate Medical Centre, Karachi, involving 70 pregnant women with confirmed CTDs. Participants were followed throughout pregnancy and postpartum. Clinical data, treatment regimens, and outcomes were recorded and analyzed.*

Results: *Rheumatoid arthritis (RA) was the most prevalent CTD, followed by systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Maternal complications included preeclampsia (53%), gestational diabetes mellitus (14%), and eclampsia (7%). Preeclampsia was most common in RA patients. Drug therapy analysis revealed that hydroxychloroquine, whether used alone or with methotrexate, was associated with increased risks of preeclampsia and GDM. Conversely, regimens including prednisolone and azathioprine were linked to better maternal outcomes.*

Fetal outcomes varied by disease type. RA patients had the highest live birth rate (n=149), yet also experienced 58 miscarriages, 15 stillbirths, and 23 cases of intrauterine growth restriction (IUGR). SLE and SS groups demonstrated higher rates of fetal compromise, including miscarriages and growth restrictions.

Conclusion: *CTDs significantly influence pregnancy outcomes. Early diagnosis, multidisciplinary care, and careful drug selection are crucial for improving maternal and fetal health in this high-risk population.*

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INTRODUCTION

Connective tissue disease (CTD) refers to a diverse array of conditions, each characterized by specific diagnostic criteria. When a patient exhibits signs and symptoms that do not completely fulfill the criteria for a specific connective tissue disease (CTD), a diagnosis of undifferentiated connective tissue disease (UCTD) is made. (1)

Autoimmune connective tissue disorders (CTD) exhibit a significant female predominance and often present before or during the reproductive years. Multiple connective tissue diseases (CTDs) have been recognized in pregnant women that may affect newborn outcomes, including dermatomyositis, systemic and cutaneous lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disease (MCTD), systemic sclerosis (SS), and Sjögren's syndrome (SS). (2-6) The systemic effects of CTDs have been thoroughly examined in the general population, although their influence on pregnancy outcomes necessitates additional research.

Live birth (71.9%), stillbirth (8.9%), miscarriage (18.7%), intrauterine growth restriction (5.4%), preeclampsia (3.9%), eclampsia (0.9%), and gestational diabetes (1.5%) according a recent study evaluating pregnancy outcomes in women with mixed connective tissue disease (MCTD). (7) Induced labor (38–64%), cesarean section (40–50%), live birth (86–92%), stillbirth (3%), miscarriage (5–10%), preterm delivery (17–28%), and preeclampsia/eclampsia (6–20%) according another study assessing pregnancy outcomes in women with SLE and UCTD. (8)

A study investigating pregnancy outcomes in women with different CTDs also found SLE, RA, and MCTD as the most common disorders (each with a frequency of 21.4%), followed by Sjögren's syndrome and systemic sclerosis (each at 7.1%) Reported negative pregnancy outcomes included preterm delivery (38.5%), stillbirth (7.1%), intrauterine growth restriction (28.6%), and preeclampsia (7.1%). (9) Given the variability in reported outcomes and the scarcity of data, particularly within Pakistani population, further research is essential to improve maternal and neonatal outcomes in pregnant women diagnosed with CTDs. A deeper understanding of these associations will facilitate early risk stratification, targeted interventions, and multidisciplinary management to optimize pregnancy outcomes in this high-risk population.

Methodology

This prospective observational study was carried out in the Department of Obstetrics and Gynecology at Jinnah Postgraduate Medical Center, Karachi, Pakistan. The required sample size of 70 participants was calculated using the WHO Sample Size Calculator, applying a 95% confidence interval, an absolute precision of 6%, and an estimated population proportion of 7.1%. The inclusion criteria encompassed women of reproductive age (15–45 years) with singleton pregnancies and a documented history of connective tissue disease (CTD) as per the operational definition. Participants were recruited either from the antenatal care outpatient department or the rheumatology clinic, including postpartum women with CTDs who were not enrolled during pregnancy. Individuals were excluded if they presented with fetal distress confirmed by a consultant obstetrician, had pre-existing hypertension or diabetes, or were diagnosed with multiple pregnancies. Ethical approval for the study was obtained from the institutional review board. All procedures followed were in accordance with the ethical standards of the responsible committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants prior to inclusion in the study.

Data Collection & Assessment

Following the acquisition of ethical approval from the institutional review board and informed consent from all participants, patients meeting the inclusion criteria were enrolled during their initial antenatal visit. Maternal baseline characteristics were documented, encompassing maternal age, gestational age, maternal blood pressure, fetal birth weight, fasting blood sugar levels, and disease duration. A comprehensive history, physical examination, and essential investigations, including complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), urine analysis (S/E and C/E), and viral markers, were conducted. Patients were monitored prospectively during pregnancy and the

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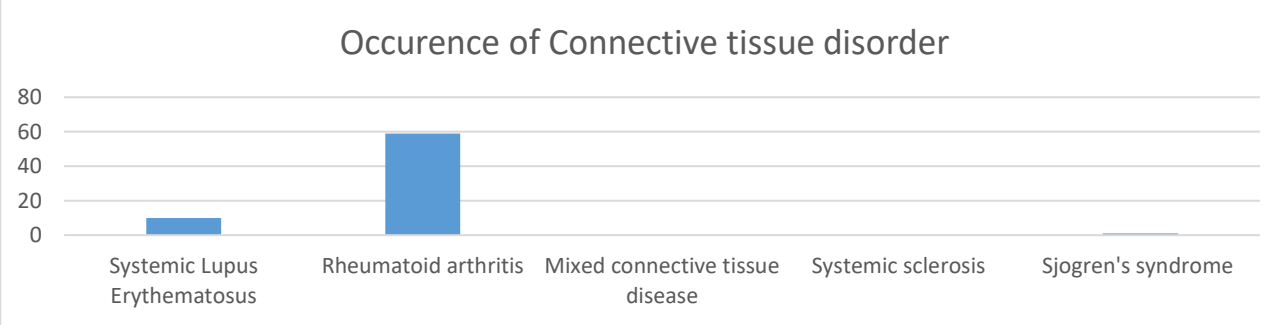
early neonatal period, extending up to 7 days post-birth. The assessed pregnancy outcomes included live birth, stillbirth, miscarriage, preterm delivery, intrauterine growth restriction (IUGR), preeclampsia, eclampsia, and gestational diabetes (GDM). Neonatal outcomes, including Apgar score, birth weight, congenital anomalies, NICU admission, and neonatal mortality, were documented.

Statistical Analysis

Data were recorded using a pre-designed proforma, and statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 26. Descriptive statistics were utilized, calculating the mean, median, and mode for continuous variables, while categorical variables were represented as frequencies and percentages. Chi-square tests were employed for categorical comparisons, while t-tests or Mann-Whitney U tests were utilized as appropriate. This study evaluates maternal and fetal outcomes in pregnant women with connective tissue diseases, aiming to enhance management strategies and obstetric care. Patient anonymity was preserved during the study.

Results

The data was collected in the form of frequencies and percentages when appropriate. SPSS version 30 was used to evaluate mean, mode, and median. From a total of 70 cases studied at JPMC hospital, authors noted that rheumatoid arthritis was the most prevalent among all connective tissue disorders in pregnancy followed by systemic lupus erythematosus. (Graph 1).



Maternal medical outcomes in patients with connective tissue disorders in pregnancy

Authors noted that out of 70 patients with connective tissue disorders, 52 had associated with medical conditions in the figure below. The most common of them were pre-eclampsia seen in 53%. Out of 37 pre-eclampsia patients, 31 had rheumatoid arthritis being the most common connective tissue disorder associated with pre-eclampsia. Second commonest condition was gestational diabetes mellitus seen in 14% of these patients. The least common were to be eclampsia patients, which constituted around 7%.

In systemic lupus erythematosus, out of 8 patients, 5 of them were associated with pre-eclampsia, 2 had gestational diabetes mellitus and 1 had eclampsia. In rheumatoid arthritis, out of 43 patients, 31 were associated with pre-eclampsia, 4 were associated with eclampsia and 8 had gestational diabetes mellitus. In Sjogren's syndrome, only 1 patient was present and was presented with pre-eclampsia. (Table 1)

	Systemic lupus erythematosus	Rheumatoid Arthritis	Sjogren's syndrome
Pre-eclampsia	5	31	1
Eclampsia	1	4	0
Gestational diabetes mellitus	2	8	0

Fetal outcome in connective tissue disorder

In Systemic Lupus Erythematosus, the live birth rate was relatively low with 16 in total, with miscarriage with 19 in total and being the most frequent adverse fetal outcome, followed by stillbirth in 6 instances. Preterm delivery occurred at 4 instances and

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intrauterine growth restriction (IUGR) arise in 2 cases, less common but still present.

In contrast, Rheumatoid Arthritis showed a higher live birth rate in 149 occasions, though there were still occurrences of miscarriage 58 times and stillbirth in 15 cases. Preterm deliveries turned out in 23 cases, and IUGR occurred in 22 instances which were more frequent in RA compared to SLE.

In contrast, Sjogren's Syndrome (SS) was linked to the most favorable fetal outcomes, as all three cases resulted in live births without any instances of stillbirth, miscarriage, preterm delivery, or intrauterine growth restriction (IUGR). These observations indicate that systemic lupus erythematosus (SLE) is associated with a higher risk of fetal loss, rheumatoid arthritis (RA) demonstrates comparatively better but still concerning outcomes, while SS, despite the limited number of cases was not associated with any negative fetal events. (Table 2)

	Systemic lupus erythematosus	Rheumatoid arthritis	Sjogren's syndrome
IUGR	2	22	0
Livebirth	16	149	3
Stillbirth	6	15	0
Preterm delivery	4	23	0
Miscarriage	19	58	0

Maternal outcomes and treatment taken

Among those who developed pre-eclampsia, the highest prevalence was observed in individuals receiving hydroxychloroquine at a dose of 200 mg, with 15 patients affected. This was followed by those on a combination therapy of hydroxychloroquine at 200 mg and methotrexate at 2.5 mg, where 12 patients were diagnosed with pre-eclampsia. A smaller proportion of individuals receiving hydroxychloroquine combined with salazodine, comprising 3 patients, or methotrexate alone at 2.5 mg, with only 1 patient affected, also developed pre-eclampsia. In contrast, no cases of pre-eclampsia were reported among individuals treated with prednisolone in combination with hydroxychloroquine and azathioprine.

In the case of eclampsia, the highest number of occurrences was seen among individuals treated with hydroxychloroquine monotherapy at 200 mg, with 3 patients affected. This was followed by a combination therapy of hydroxychloroquine at 200 mg and methotrexate at 2.5 mg, where 2 patients developed eclampsia. No cases were reported in individuals receiving other therapeutic regimens, suggesting a potentially lower risk among those on combined immunosuppressive treatments.

Regarding gestational diabetes mellitus, the highest frequency was noted among individuals on hydroxychloroquine monotherapy at 200 mg, where 4 patients developed the condition. An equal number of cases were also observed among those receiving a combination therapy of hydroxychloroquine at 200 mg and methotrexate at 2.5 mg. A single occurrence of gestational diabetes mellitus was identified in an individual on hydroxychloroquine combined with salazodine. However, no individuals receiving methotrexate alone, prednisolone-based combinations, or hydroxychloroquine with azathioprine developed gestational diabetes mellitus.

These findings suggest that the use of hydroxychloroquine at 200 mg, particularly as monotherapy or in combination with methotrexate, is associated with a higher prevalence of pre-eclampsia and gestational diabetes mellitus. Additionally, eclampsia was more frequently observed among those on hydroxychloroquine monotherapy. Other treatment combinations, particularly those involving prednisolone and azathioprine, appeared to be associated with fewer adverse maternal outcomes. (Graph 2)

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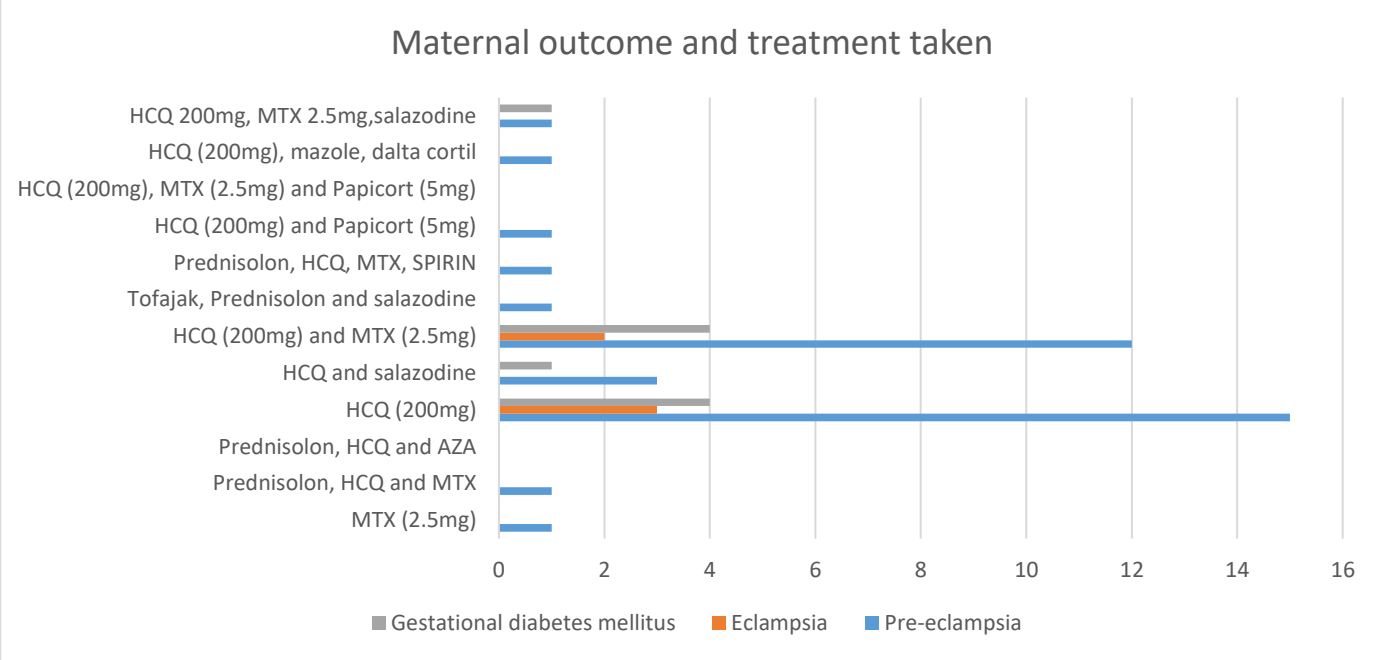

Fetal outcomes and treatment taken

Among those who experienced IUGR, the highest number of patients were observed while receiving hydroxychloroquine (200 mg), 11 patients were noted. This was followed by those on hydroxychloroquine (200 mg) combined with methotrexate (2.5 mg), 7 patients had it. In contrast, IUGR was less frequent in other treatment groups, with 1 patient reported receiving methotrexate alone, hydroxychloroquine with salazodine, or hydroxychloroquine with methotrexate and papicort. 0 patients of IUGR were reported in those on prednisolone-based regimens or hydroxychloroquine in combination with azathioprine.

Live births had the following results: hydroxychloroquine (200 mg) was associated with the highest number of successful deliveries, with 64 instances. A considerable number of live births were also recorded in those treated with hydroxychloroquine (200 mg) in combination with methotrexate (2.5 mg), where 54 livebirths occurred. Other treatment groups, including methotrexate alone had 17 patients, hydroxychloroquine with salazodine had 8 births, and a combination of hydroxychloroquine with prednisolone and salazodine gave 6 births, also showed relatively high live birth rates. The lowest live birth rates were observed in that receiving prednisolone with hydroxychloroquine and azathioprine, prednisolone with hydroxychloroquine, methotrexate, and SPIRIN, and hydroxychloroquine with methotrexate and papicort, all reported 2 livebirths.

In the case of stillbirths, hydroxychloroquine (200 mg) was associated with the highest number, with 8 occurrences reported. This was followed by hydroxychloroquine (200 mg) in combination with methotrexate (2.5 mg), where 5 instances were observed. Receiving methotrexate alone showed 4 instances, hydroxychloroquine and methotrexate with papicort 1 occurrence, and hydroxychloroquine in combination with methotrexate, mazole, and delta cortil had 1 instance. No stillbirths were recorded in those receiving prednisolone-based combinations or hydroxychloroquine with salazodine.

For preterm delivery, hydroxychloroquine (200 mg) was again the most frequently associated treatment, with 13 individuals experiencing preterm birth. A smaller number of cases were reported in that receiving hydroxychloroquine with methotrexate (2.5 mg) had 4 cases and methotrexate monotherapy had 4 cases. Other treatment groups; including hydroxychloroquine with salazodine, hydroxychloroquine with methotrexate and papicort, and hydroxychloroquine with methotrexate, mazole, and delta cortil, reported 1 case only. No preterm

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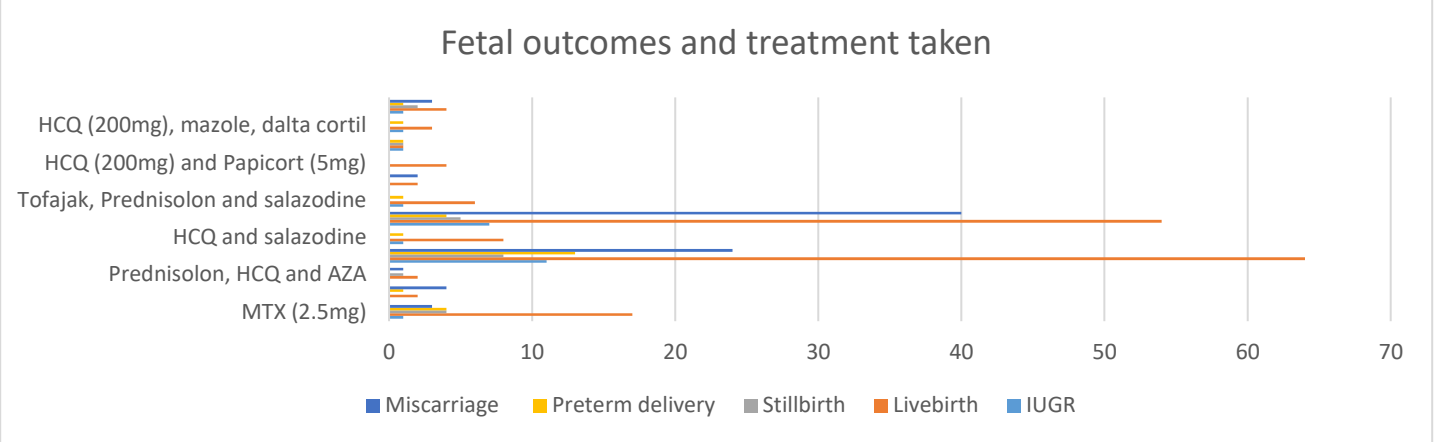
deliveries were noted among individuals receiving prednisolone-based regimens.

With respect to miscarriage, the highest number of occurrences was observed among those on hydroxychloroquine (200 mg) in combination with methotrexate (2.5 mg), with 40 cases documented. Hydroxychloroquine monotherapy (200 mg) was associated with 24 cases of miscarriage, while methotrexate alone resulted in 3 cases. Women on prednisolone with hydroxychloroquine and methotrexate had 4 cases, prednisolone with hydroxychloroquine and azathioprine had 1 instance, and prednisolone with hydroxychloroquine, methotrexate, and SPIRIN had 2 occurrences. No miscarriages were recorded in women receiving hydroxychloroquine with salazodine. (Graph 3).



Discussion:

Connective tissue diseases (CTDs), a diverse group of autoimmune disorders, are characterized by chronic immune-mediated inflammation that damages tissues and can lead to organ dysfunction. Conditions such as scleroderma, dermatomyositis, and systemic lupus erythematosus (SLE) share similar immunopathogenic mechanisms arising from dysregulated immune responses (10,11). The diagnostic approach for CTDs is multidisciplinary, involving serological testing, imaging, and clinical evaluation. Autoantibody profiles, including antinuclear antibodies (ANA), are crucial in establishing diagnoses, while imaging techniques such as X-rays and MRI help assess anatomical and structural changes. Diagnostic accuracy is further improved by incorporating tissue biopsies, pulmonary function testing, and echocardiography, with collaborative input from various specialties ensuring optimal patient care (12).

Autoimmune CTDs predominantly affect women, particularly during their childbearing years, creating unique reproductive health challenges. Diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), systemic sclerosis (SSc), primary Sjögren's syndrome (PSS), and idiopathic inflammatory myopathies commonly present during this life stage, complicating pregnancy planning and management (14). Research indicates that adverse fetal outcomes are notably more prevalent among pregnant women with CTDs. For instance, mothers with SLE and RA have a higher incidence of delivering small-for-gestational-age infants compared to the general obstetric population, alongside elevated rates of preterm birth, intrauterine growth restriction (IUGR), and fetal loss (13).

Pregnancy Outcomes in Systemic Lupus Erythematosus (SLE):

SLE is a chronic autoimmune condition that affects multiple organ systems and exhibits unpredictable flares and remissions. Thanks to advancements in disease management, the life expectancy of individuals with SLE has improved. However, while pregnancy is often tolerated, the postpartum period poses a significant risk for disease flares, underscoring the importance of long-term follow-up and postpartum disease surveillance (14,15).

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A study by D.E.A. Pastore et al. revealed that pregnant women with SLE frequently encounter maternal and fetal complications. Flares during pregnancy were closely associated with preterm labor and premature birth. The study reported a mean maternal age of 27.7 years and that nearly half of the participants were primigravidas. Among these women, 46.8% delivered preterm (average gestational age 34.4 weeks), and pre-pregnancy lupus activity was a significant predictor of poor outcomes, including pregnancy loss and delivery before 34 weeks (16). In patients with juvenile idiopathic arthritis (JIA), although most pregnancies resulted in live births, prematurity and disease flares during pregnancy and postpartum were frequently observed, particularly in those who discontinued biologics (17).

Larissa Rodrigues et al. studied 82 pregnancies in women with SLE and found a fetal loss rate of 15.8%, a preterm delivery rate of 34.1%, and small-for-gestational-age infants in 8.5% of cases. The presence of antiphospholipid antibodies was associated with worse fetal outcomes, whereas low disease activity at conception showed a protective effect (15). Another cohort of 69 pregnancies reported high rates of disease flares (39.2%), with renal involvement and severe disease activity significantly contributing to maternal and fetal complications, including a 3% maternal mortality rate and high perinatal death in those with elevated SLEDAI scores (18).

Data from a tertiary care hospital in Karachi emphasized that well-planned pregnancies and controlled disease activity led to improved feto-maternal outcomes. Nevertheless, the study reported third-trimester flare-ups in over half the patients, and maternal complications such as preeclampsia and eclampsia remained prevalent. Cesarean deliveries were common, and fetal risks included high rates of preterm birth, IUGR, and neonatal mortality (19). These findings strongly advocate for careful disease control before conception and throughout pregnancy. Immunosuppressive regimens must be tailored to balance maternal disease control with fetal safety, as unchecked disease activity poses serious risks (20).

Pregnancy Outcomes in Rheumatoid Arthritis (RA):

RA is a systemic inflammatory disorder that predominantly affects joints but may also involve other organs. Women are disproportionately affected, particularly during their reproductive years (21). Despite improvements in disease management, pregnant women with RA continue to face increased risks of complications such as hypertensive disorders, IUGR, preterm birth, and cesarean deliveries. Achieving remission or low disease activity prior to pregnancy significantly reduces these risks, although a residual risk still remains (21,22).

In a large comparative study, RA patients demonstrated higher rates of miscarriage, perinatal mortality, and adverse pregnancy outcomes (APOs) compared to the general population. However, women receiving appropriate management, including medications like low-molecular-weight heparin (LMWH), showed a notable reduction in these risks (23).

Fertility and time-to-pregnancy (TTP) are also affected in RA. One study comparing women with RA and SLE found that RA patients had a significantly prolonged TTP, with more than a third classified as subfertile. Live birth rates were lower in RA patients, and a significant portion remained unable to conceive (24). Additional evidence from a study examining 132 pregnancies found that RA patients were more likely to experience adverse outcomes such as preterm delivery, emergency C-sections, and fetal growth restriction, emphasizing the role of disease activity and treatment regimens in shaping pregnancy outcomes (25).

Despite the global burden of CTDs, there is a scarcity of region-specific research in Pakistan regarding their implications during pregnancy. This study is among the first comprehensive investigations into pregnancy outcomes in Pakistani women with CTDs. Bridging this knowledge gap is vital for improving preconception counseling, enabling informed family planning, and ensuring appropriate prenatal monitoring. However, some limitations must be acknowledged: the sample size was relatively small, the cohort was skewed toward patients with SLE and RA, and those requiring urgent medical intervention were excluded, possibly underestimating the full scope of pregnancy-related complications in

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this population. Future studies should focus on broader and more diverse patient groups to better capture the spectrum of CTDs and their impact on maternal and fetal health in the local context.

Sociocultural dynamics in Pakistan may further influence disease management, awareness, and access to care. Therefore, context-specific strategies are needed to improve outcomes in this vulnerable population.

Conclusion:

In conclusion, effective management of pregnancy in women with connective tissue diseases hinges on disease remission prior to conception, ongoing postpartum surveillance, and individualized care plans. Immunosuppressive therapy must be judiciously adjusted to control maternal disease while minimizing fetal risks. Multidisciplinary collaboration among obstetricians, rheumatologists, and neonatologists is vital to optimize maternal and neonatal outcomes in this high-risk group.

Authorship Statement

We affirm that this manuscript is an original piece of work and has not been submitted for publication or considered by any other journal.

Ethical Approval

Approval for this research was granted by [insert institution/ethics committee name] in compliance with applicable ethical guidelines.

Conflict of Interest

We confirm that there are no conflicts of interest that could be seen as influencing the impartiality of this research.

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During the preparation of this manuscript, the author utilized the CHATGPT 3.5 version to assist with language and grammar refinement. The author has thoroughly reviewed and edited the content and assumes full responsibility for the final version of the publication.

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