Pregnancy outcomes in connective tissue diseases: a 30-year study of 465 cases from a single-center Spanish registry with insights on hydroxychloroquine use

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Abstract

Introduction: Pregnancy in women with connective tissue diseases (CTDs), including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), primary Sjögren's syndrome (pSS), and undifferentiated connective tissue disease (UCTD), poses significant risks for adverse outcomes. Evaluating these risks and outcomes is essential to improve maternal and fetal health.

Objectives: This study aimed to assess pregnancy outcomes in patients with CTDs, identify factors associated with adverse outcomes, and evaluate the protective effects of hydroxychloroquine (HCQ) treatment.

Methods: A study covering the period from 1990 to 2022 was conducted. Data were collected from medical records of childbearing-age women with SLE, SSc, pSS, and UCTD who were under care at our clinic. Obstetric, maternal, and fetal outcomes were analyzed across different diagnoses. Statistical analyses were performed to identify associations between disease activity, treatments, and pregnancy outcomes.

Results: A total of 295 patients (125 with SLE, 50 with SSc, 80 with pSS, and 40 with UCTD) and 465 pregnancies were included. The mean age at first pregnancy was 29.1±9.1 years. Pregnancy loss occurred in 21% of cases, while 77% resulted in live births. Adverse outcomes included preterm delivery (8%), postpartum hemorrhage (6%), and preeclampsia (5%). SLE diagnosis (OR 1.5, 95% CI [1.1–4.8], p = 0.03), double/triple antiphospholipid antibody (APL) positivity (OR 2.3, 95% CI [1.1–3.9], p = 0.04), and active disease (OR 3.4, 95% CI [1.8–5.2], p = 0.004) were identified as risk factors for adverse pregnancy outcomes. HCQ treatment demonstrated a protective effect (OR 0.34, 95% CI [0.05–0.72], p = 0.0004).

Conclusion: Two-thirds of pregnancies in women with CTDs resulted in live births, though SLE was associated with significantly higher risks. Active disease during pregnancy emerged as a major risk factor. Importantly, the use of HCQ was associated with a notable reduction in these risks, underscoring its protective role in improving pregnancy outcomes. These findings highlight the critical importance of preconception counseling, careful disease management, and the proactive use of HCQ to minimize complications and optimize outcomes in pregnancies complicated by CTDs.

Keywords: Epidemiology; Hydroxycholoroquine; Pregnancy and rheumatic disease; Systemic lupus erythematosus and autoimmunity; Immunosuppressants.

Introduction

Pregnancy in women with autoimmune diseases presents unique challenges due to the increased risk of maternal and obstetric complications[1]. These pregnancies are often categorized as high-risk because autoimmune conditions, such as connective tissue diseases (CTDs), can impact both maternal health and pregnancy outcomes. Women with autoimmune diseases are at a higher risk for complications such as preterm birth, preeclampsia, fetal growth restriction, and disease exacerbations during pregnancy. Monitoring disease activity and maintaining disease control with safe treatments are crucial to ensuring favourable outcomes for both mother and baby[2].

Preconception counselling plays a vital role in improving pregnancy outcomes for women with autoimmune diseases, particularly those with CTDs[3]. By providing detailed guidance on the risks and complexities associated with pregnancy in the context of their specific condition, women can make informed decisions about family planning. Additionally, preconception counselling offers an opportunity to optimize disease management before conception, reducing the risk of adverse pregnancy outcomes [4,5]. Effective collaboration between rheumatology and obstetrics is essential for managing these complex pregnancies. Recent guidelines from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) emphasize the importance of safe therapies during pregnancy and breastfeeding[6,7]. The updated EULAR Points to Consider (PtC) for the use of antirheumatic drugs in reproduction, pregnancy, and lactation address critical aspects of managing such pregnancies. These guidelines, provide detailed recommendations on compatible antirheumatic treatments, balancing maternal disease control with fetal safety[8].

In this study, we conducted an observational case-control analysis to evaluate pregnancy outcomes in patients with CTDs, including SLE, SSc, pSS, and UCTD, and to determine the demographic, clinical, and serological characteristics associated with adverse pregnancy outcomes.

Methods

Patients

We conducted a cohort study involving 295 patients diagnosed with CTDs, including systemic lupus erythematosus (SLE), Sjögren's syndrome (SjS), systemic sclerosis (SSc), and undifferentiated connective tissue disease (UCTD), all with a history of pregnancy. The study spanned from 1990 to 2022 and was carried out within our systemic autoimmune diseases' unit. While classification criteria were used for research purposes, all diagnoses were confirmed by experienced physicians to ensure clinical accuracy. CTD classification was based on established criteria: the 1997 ACR and 2019 EULAR criteria for SLE, the 2016 EULAR criteria for pSS, and the 2013 EULAR criteria for SSc[9-12]. UCTD was defined by clinical symptoms indicative of systemic autoimmune disease and laboratory evidence of autoimmunity, without meeting specific classification criteria for any recognized autoimmune disorder[13].

Clinical and immunological data

Clinical data for all patients were collected through a comprehensive review of medical records. Key sociodemographic information, including age at diagnosis, age at first pregnancy, and disease duration, was documented. Cardiovascular risk factors such as smoking were recorded alongside pregnancy treatments to evaluate their influence on maternal and fetal health. Maternal and fetal complications were meticulously documented, enabling robust analyses of associations between CTDs, treatment, and pregnancy outcomes. A thorough collection of clinical data was performed to capture the manifestation and progression of CTDs, including analytical, serological, and immunological parameters, such as acute phase reactants. Antiphospholipid antibodies were evaluated in detail: anticardiolipin antibodies (aCL) were classified as positive if titers exceeded 40 GPL or MPL units on two or more occasions at least 12 weeks apart, consistent with the 2006 Sydney criteria for antiphospholipid syndrome (APS). Lupus anticoagulant (LA) testing adhered to International Society on Thrombosis and Haemostasis (ISTH) guidelines, with LA positivity confirmed by two separate positive tests 12 weeks apart[14]. Anti-beta2 glycoprotein I (anti-β2GPI) antibodies (IgG and/or IgM) were measured using enzyme-linked immunosorbent assay (ELISA), with a positivity threshold above the 99th percentile of healthy controls, and persistent positivity confirmed after 12 weeks. While serological data were available for the majority of patients, some data were missing due to incomplete registries. Maternal and fetal complications, including pregnancy-related outcomes, were meticulously documented, allowing for a robust analysis of the associations between CTDs, treatment, and pregnancy outcomes.

Definitions

Active disease was defined as the exacerbation or onset of symptoms associated with CTDs before pregnancy. Hypertension was diagnosed when systolic blood pressure exceeded 140 mmHg and/or diastolic blood pressure exceeded 90 mmHg in at least two consecutive measurements taken in a seated position during pregnancy. Preeclampsia was identified by the development of hypertension, often accompanied by proteinuria, after the 20th week of gestation in a woman who was previously normotensive. Eclampsia was described as the occurrence of one or more generalized tonic-clonic seizures in women with a hypertensive pregnancy disorder, not attributed to other medical conditions. Fetal loss included spontaneous abortion, therapeutic abortion, intrauterine fetal death (IUFD), and neonatal death. Premature delivery was defined as birth occurring before 37 weeks of gestation. Ectopic pregnancy referred to implantation occurring outside the uterus. Postpartum hemorrhage was characterized by excessive bleeding from the birth canal following childbirth. Preterm premature rupture of membranes (PROM) was defined as the spontaneous rupture of membranes before 37 weeks of gestation, which could lead to complications and risks for the fetus. Placental abnormalities encompassed conditions such as placenta previa (where the placenta partially or completely obstructs the cervix), placental abruption (premature separation of the placenta from the uterine wall), placenta accreta (abnormal adherence of the placenta to the uterine wall), and placental infarction (areas of necrosis or tissue death within the placenta).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation when normally distributed. For comparisons between two groups, the Mann-Whitney U test or Student's t-test was applied, depending on the data distribution. When comparing more than two groups, ANOVA was used for normally distributed data, while the Kruskal-Wallis test was applied for non-parametric data. Univariate analyses were performed to assess clinical, serological, and immunological predictors. Variables identified as potential predictors in the univariate analysis were then included in multivariate models using stepwise selection. Statistical significance was set at $p < 0.05$ for all analyses, which were conducted using SPSS version 22.0

Results

Sociodemographic characteristics

This study included 295 patients diagnosed with CTDs, comprising 125 (42%) with SLE, 50 (17%) with SSc, 80 (27%) with pSS, and 40 (14%) with UCTD. A total of 495 pregnancies were identified: 192 in SLE patients, 88 in SSc patients, 120 in pSS patients, and 65 in UCTD patients. The mean age at diagnosis was 28.2±7.2 years, while the mean age at first pregnancy was 29.1±9.1 years, with a mean disease duration of 7.2±5.6 years. The mean gestational age was 37.2 weeks (range 27–40 weeks). Of the pregnancies, 44 (32.5%) were primiparous, and 358 (77%) resulted in live births. Smoking history was reported in 86 (29%) patients, while 10 (3%) had diabetes, 15 (5%) had hypertension, 20 (7%) had dyslipidaemia, and 45 (15%) were obese.

Clinical and immunological characteristics

Table I presents the clinical, immunological, and treatment differences among the diseases. Arthritis and glomerulonephritis were more prevalent in SLE patients ($p=0.03$ and $p<0.001$, respectively), while pulmonary hypertension and interstitial lung disease (ILD) were more common in SSc patients ($p<0.001$). No significant differences were observed in the mean age at first pregnancy or the presence of serositis and arterial and/or venous thrombosis across the diseases.

During pregnancy, hydroxychloroquine (HCQ) was prescribed to 98 (78%) SLE patients, 18 (14%) SSc patients, 52 (65%) pSS patients, and 14 (35%) UCTD patients ($p<0.001$). The average HCQ dose was 312 mg/day, with no significant differences in dosage across disease groups. Lupus anticoagulant (LA) was positive in 59 (47%) SLE patients, 12 (24%) SSc patients, 7 (8.8%) pSS patients, and 7 (18%) UCTD patients ($p=0.004$). Anti-beta2-glycoprotein antibodies were positive in 17 (14%) SLE patients, 1 (2%) SSc patient, 1 (1%) pSS patient, and 4 (10%) UCTD patients ($p<0.001$). Double or triple antiphospholipid antibody positivity was more frequent in SLE patients ($p<0.001$). No significant differences were found for anti-Ro/SSA, anti-La/SSB, anti-RNP, anticardiolipin, low complement C4 levels, or acute phase reactants among the diseases.

Aspirin was used by 32 (26%) SLE patients, 8 (16%) SSc patients, 4 (8%) pSS patients, and 3 (8%) UCTD patients. Corticosteroids were used by 17 (14%) SLE patients, 5 (4%) SSc patients, 8 (16%) pSS patients, and 3 (8%) UCTD patients. Biologic treatments were administered to 5 (4%) SLE patients, 1 (2%) SSc patient, and 3 (4%) pSS patients. Active disease before conception was reported in 32 (26%) SLE patients, 14 (28%) SSc patients, and 2 (2.5%) pSS patients.

Pregnancy outcomes in CTDs

Table II provides an overview of pregnancy characteristics across CTDs, while Figure 1 highlights disparities between SLE and non-SLE patients. Of the 495 pregnancies analysed, 192 (41%) were associated with SLE, 88 (19%) with SSc, 120 (26%) with pSS, and 65 (14%) with UCTD. A majority, 263 (57%), were considered normal pregnancies. However, complications included 97 (21%) pregnancy losses, 87 (19%) abortions, 6 (1%) intrauterine fetal demise, 25 (5%) preeclampsia, 35 (8%) preterm deliveries, 30 (6%) cases of postpartum haemorrhage, 18 (4%) placental abnormalities, 15 (3%) ectopic pregnancies, 10 (2%) premature ruptures of membranes and 11 (2%) cases of maternal deaths.

SLE patients had significantly higher rates of fetal loss (30%) compared to SSc (14%), pSS (15%), and UCTD (15%) (p=0.03). Similarly, preeclampsia (9% in SLE vs. 3% in SSc, 2% in pSS, and 3% in UCTD, p=0.03), preterm delivery (13% in SLE vs. 6% in pSS and 8% in UCTD, p=0.02), and postpartum haemorrhage (11% in SLE vs. 5% in SSc vs 1% in pSS and 3% in UCTD, p=0.01) were more frequent in SLE. Maternal mortality was higher in SSc compared to other CTDs (p=0.04).

Comparative analysis of pregnancies before and after the year 2000 is detailed in Table III. Between 1980–2000, 201 pregnancies were recorded, while 265 occurred between 2001–2020. Pregnancies after 2000 were characterized by older maternal age at conception (p=0.03). Outcomes improved significantly in the later period, with higher live birth rates (OR 0.34, 95% CI 0.25–0.60, p<0.0001) and lower rates of abortion, ectopic pregnancies, postpartum haemorrhage, and maternal mortality.

Predictors of adverse pregnancy outcomes

Table IV represents the predictor factors of adverse pregnancy outcomes. Univariate and multivariate analyses identified significant predictors of adverse pregnancy outcomes. SLE diagnosis (OR 2.8, 95% CI 1.3–5.4, p=0.04), SSc diagnosis (OR 1.4, 95% CI 1.1–4.3, p=0.04), double or triple APL positivity (OR 2.4, 95% CI 1.24–4.2, p=0.03), low complement levels (OR 1.5, 95% CI 1.1–3.4, p=0.04), active disease prior to pregnancy (OR 3.5, 95% CI 2.1–5.6, p=0.002), and glomerulonephritis (OR 3.1, 95% CI 2.4–5.8, p=0.02) were associated with adverse outcomes. HCQ treatment demonstrated a protective effect (OR 0.43, 95% CI 0.14–0.89, p=0.002).

In the multivariate analysis, SLE diagnosis (OR 1.5, 95% CI 1.1–4.8, p=0.03), double or triple APL positivity (OR 2.3, 95% CI 1.1–3.9, p=0.04), and active disease (OR 3.4, 95% CI 1.8–5.2, p=0.004) remained significant predictors of adverse outcomes, while HCQ treatment retained its protective effect (OR 0.34, 95% CI 0.05–0.72, p=0.0004).

Discussion

Our study, which included 295 patients with CTDs such as SLE, SSc, pSS, and UCTD, provided valuable insights into maternal and fetal outcomes. It highlighted that pregnancy in women with CTDs carries significant risks, with adverse outcomes being more common in patients with active disease.

In this cohort, 263 pregnancies (53%) had normal outcomes. However, complications were notable: 99 pregnancies (20%) ended in loss, 35 (7%) resulted in preterm delivery, 30 (6%) experienced postpartum hemorrhage, 25 (5%) were complicated by preeclampsia, 20 (4%) exhibited placental abnormalities, 15 (3%) involved ectopic pregnancies, and 10 (2%) had premature rupture of membranes. These findings underscore the inherent risks of pregnancy in women with CTDs and the importance of meticulous preconception counseling and disease management.

Univariate and multivariate analyses identified several predictors of adverse pregnancy outcomes, including antiphospholipid (aPL) positivity, low complement levels, active disease before conception, and elevated erythrocyte sedimentation rate. Conversely, treatment with hydroxychloroquine (HCQ) and aspirin demonstrated protective effects against adverse outcomes.

The use of HCQ significantly reduced the risk of adverse pregnancy outcomes among women with CTDs. Its immunomodulatory properties help control inflammation and reduce disease flares during pregnancy, leading to improved maternal and fetal outcomes. In SLE, where active disease increases the risks of preterm birth, preeclampsia, and fetal loss, HCQ has been particularly beneficial. Furthermore, HCQ's safety profile during pregnancy—marked by no increase in congenital malformation risk—supports its role as a cornerstone of treatment. It is important to note that while higher dosages may pose potential risks, these are not relevant in standard clinical practice, where the benefits of HCQ far outweigh any theoretical concerns.

Integrating HCQ into preconception planning and disease management can stabilize disease activity, reduce complications such as hypertension and preeclampsia, and improve overall outcomes for both mother and child. While HCQ's benefits in SLE pregnancies are well-documented, its effects on other CTDs remain less clear. However, studies suggest that HCQ may improve pregnancy outcomes and disease course in women with various CTDs 27,28,30,33. HCQ seems to increase the live birth rate in pregnant women with persistent positive aPL and reduce the incidence of preeclampsia, pregnancy hypertension and PTB in those with SLE, and to decrease the occurrence of congenital heart block in anti-SSA/Ro-positive mothers.23,24 The use of HCQ in pregnant patients with UCTD is relatively unknown. Preliminary data have suggested good pregnancy outcomes and high birth rates when UCTD patients with pregnancy loss were treated with a combination of HCQ, low-dose prednisone and anticoagulation [31,32,34].

Preconception counselling and shared decision-making are vital for managing pregnancies in women with CTDs. These approaches allow for personalized care and ensure optimal disease control before, during, and after pregnancy. Active disease during pregnancy emerged as a strong predictor of adverse outcomes, emphasizing the importance of achieving remission or low disease activity prior to conception. Planning pregnancies during periods of disease quiescence can significantly mitigate risks, providing a safer environment for both mother and child.

Specific risk factors for adverse outcomes include active or flaring disease, active nephritis, and glucocorticoid use[15,16,17]. Active disease during pregnancy can exacerbate maternal health complications, increasing the risks of preterm delivery, preeclampsia, and pregnancy loss. Active nephritis, characterized by severe renal involvement in CTDs, poses additional threats such as hypertension, proteinuria, and impaired kidney function[18,19]. Discontinuing HCQ during pregnancy has been associated with an increased risk of SLE flares [20,21,22,23].

Double and triple aPL positivity were significant risk factors for adverse outcomes. aPL positivity is a well-established predictor of both thrombosis and adverse pregnancy outcomes in primary antiphospholipid syndrome (APS)[24,25]. The PREGNANTS cohort study reported lower live birth rates and higher incidences of intrauterine growth restriction (IUGR) in women with triple aPL positivity compared to those with double positivity without lupus anticoagulant (LA)[26].

Temporal analysis revealed evolving trends, with pregnancies after 2000 characterized by older maternal age at conception. Encouragingly, this period saw improvements in several metrics, including higher live birth rates and reduced incidences of abortion, ectopic pregnancy, postpartum hemorrhage, and maternal mortality. These trends highlight advancements in pregnancy management for women with CTDs.

However, this study's reliance on previously collected data presents limitations, including potential biases due to incomplete or missing records. Although the sample size is substantial, it may not fully capture the diversity of populations with CTDs, as the majority of patients had SLE, which could influence the findings. Additionally, the single-center design restricts the applicability of the results to other settings with different patient populations and management practices. Variations in disease duration, treatment regimens, and monitoring across the cohort could also impact the outcomes.

Despite its limitations, this study offers a comprehensive analysis of sociodemographic, clinical, immunological, and treatment factors influencing pregnancy outcomes in CTDs. By adjusting for confounders in multivariate analyses, it highlights independent predictors of adverse outcomes and underscores the need for individualized management strategies.

Future research should focus on prospective studies to establish causal relationships and minimize biases. Expanding to include more diverse populations and multi-center data will enhance the generalizability of findings. Long-term studies evaluating maternal and child health post-pregnancy are also essential to understand the lasting impacts of CTDs and their treatments. This study reinforces the critical importance of tailored care for pregnant women with CTDs. By identifying risk factors and highlighting the protective effects of HCQ, it underscores the pivotal role of this treatment in improving pregnancy outcomes. These findings emphasize the need for continued research, vigilant management, and the integration of HCQ into care strategies to optimize outcomes for this vulnerable population.

Tables and Figures

Table I – Clinical, immunological and serological characteristics of patient

	SLE	SSc	pSS	UCTD	P value
Mean age at first pregnancy (mean±SD)	29.5±9.2 years	31.3±10.2 years	28.5±6.2 years	29.8±9.6 years	0.57
Arthritis (%)	52 (42%)	14 (28%)	14 (18%)	8 (20%)	**0.03**
Glomerulonephritis (%)	42 (33%)	3 (6%)	13 (16%)	3 (8%)	**<0.001**
Pulmonary hypertension (%)	5 (3%)	10 (20%)	2 (3%)	0	**<0.001**
ILD (%)	3 (2%)	8 (16%)	7 (9%)	0	**<0.001**
Serositis (%)	21 (17%)	6 (12%)	0	5 (13%)	0.72
Arterial thrombosis (%)	12 (10%)	4 (8%)	2 (3%)	1 (3%)	0.62
Venous thrombosis (%)	17 (14%)	7 (14%)	2 (3%)	5 (13%)	0.56
HCQ (%)	98 (78%)	18 (14%)	52 (65%)	14 (35%)	**<0.001**
AAS (%)	32 (26%)	8 (16%)	4 (8%)	3 (8%)	0.27
Heparin (%)	10 (8%)	2 (4%)	0	0	0.18
Corticosteroids (%)	17 (14%)	5 (4%)	8 (16%)	3 (8%)	0.78
Biologics (%)	5 (4%)	1 (2%)	3 (4%)	0	0.68
Active disease (%)	32 (26%)	14 (28%)	2 (2.5%)	0	**0.03**
Anti-DNAds (%)	58 (46%)	3 (6%)	8 (10%)	12 (30%)	**<0.001**
Anti-SM (%)	21 (17%)	0	1 (1%)	3 (8%)	**<0.001**
Anti-SSA (%)	14 (11%)	18 (36%)	45 (57%)	18 (45%)	0.42
Anti-SSB (%)	2 (2%)	1 (2%)	35 (44%)	12 (30%)	0.19
Anticentromere (%)	1 (0.8%)	27 (54%)	8 (10%)	17 (43%)	**0.03**
Antitopoisomerase (%)	9 (7%)	18 (36%)	2 (2.5%)	6 (15%)	**<0.001**
Anti-RNP (%)	15 (12%)	4 (8%)	2 (2.5%)	5 (13%)	0.87
Lupus anticoagulant(%)	59 (47%)	12 (24%)	7 (8.8%)	7 (18%)	**0.004**
Anticardiolipin (%)	25 (20%)	10 (20%)	3 (4%)	4 (10%)	0.67
Beta2glicroprotein (%)	17 (14%)	1 (2%)	1 (1%)	4 (10%)	**<0.001**
Doble/Triple APL positivity (%)	31 (25%)	5 (10%)	1 (1)	2 (5%)	**<0.001**
Low C3 (%)	69 (55%)	9 (18%)	18 (23%)	15 (38%)	**<0.001**
Low C4 (%)	21 (17%)	1 (2%)	11 (14%)	9 (23%)	0.45
Elevated ESR (%)	29 (23%)	12 (24%)	24 (30%)	10 (25%)	0.34
Elevated CRP (%)	17 (14%)	7 (14%)	5 (6%)	6 (15%)	0.65

Table II - Characteristics of CTDs pregnancy

	SLE	SSc	pSS	UCTD	P value
Total of pregnancies	192 (41%)	88 (19%)	120 (26%)	65 (14%)	-
Age at pregnancy (mean±SD)	32.4±4.5	29.5±7.2	30.4±3.5	33.5±2.7	0.45
Smoking history (%)	32 (26%)	17 (21%)	25 (31%)	12 (30%)	0.27
Live birth (%)	141 (73%)	68 (77%)	102 (85%)	47 (72%)	0.28
Fetal loss (%)	47 (24%)	18 (20%)	18 (15%)	10 (15%)	**0.03**
Abortion (%)	43 (22%)	16 (18%)	18 (15%)	10 (15%)	**0.04**
Intrauterine fetal demise (%)	4 (2%)	2 (2%)	0	0	0.56
Mean fetal loss number	2.7±0.7	1.1±0.6	2.4±0.3	0.9±0.5	**0.03**
Preeclampsia (%)	18 (9%)	3 (3%)	2 (2%)	2 (3%)	**0.04**
Ectopic pregnancy (%)	12 (7%)	1 (1%)	1 (1%)	1 (2%)	**0.03**
Placental abnormalities (%)	8 (4%)	5 (6%)	2 (2%)	3 (5%)	0.21
Premature rupture of membranes (PROM) (%)	5 (3%)	2 (2%)	2 (2%)	1 (2%)	0.24
Preterm delivery (%)	22 (11%)	0	8 (6%)	5 (8%)	**0.02**
Postpartum haemorrhage (%)	21 (11%)	4 (5%)	4 (3%)	1 (2%)	**0.01**
Maternal death (%)	5 (4%)	5 (10%)	1 (1%)	0	**0.04**

Note: Serological data were available for the majority of patients; however, some data were missing due to incomplete registries. Percentages and values reflect the available data for each variable.

Table III - Comparative analysis between pregnancies occurring before and after the year 2000

	Pregnancies 1990-2000	Pregnancies 2001-2022	OR 95%	P value
Total of pregnancies (n)	201	265	-	-
Age at pregnancy (years)	25.4±5.6	32.5±7.2	-	**0.03**
Live birth (%)	135 (67%)	223 (84%)	0.34 (0.25-0.60)	**<0.0001**
Fetal loss (%)	62 (31%)	40 (15%)	2.9 (1.8-4.7)	**<0.0001**
Abortion (%)	58 (29%)	30 (11%)	3.3 (2.0-5.5)	**<0.0001**
Mean abortion number (mean	3.2±1.2	1.1±0.6	-	**0.03**
Intrauterine fetal demise (%)	4 (2%)	2 (0.7%)	3.4 (0.6-17.5)	0.15
Preeclampsia	12 (6%)	10 (4%)	1.6 (0.7-3.8)	0.27
Ectopic pregnancy	9 (4%)	3 (1%)	4 (1.1-15.3)	**0.002**
Placental abnormalities	10 (5%)	9 (3%)	1.5 (0.6-3.7)	0.39
Premature rupture of membranes (PROM)	5 (3%)	3 (1%)	2.2 (0.5-9.4)	0.27
Preterm delivery	17 (8%)	14 (5%)	1.7 (0.8-3.4)	0.18
Postpartum haemorrhage	18 (9%)	8 (3%)	3.2 (1.3-7.4)	**0.008**
Maternal death	10 (11%)	1 (0.5%)	13.8 (1.7-108.9)	**<0.0001**

Table IV - Univariate and multivariate analysis

		OR 95%	P value	OR 95%	P value
	SLE	2.8 (1.3-5.4)	**0.04**	1.5 (1.1-4.8)	**0.03**
	SSc	1.4 (1.1-4.3)	**0.04**	1.1 (0.76-3.4)	0.76
	pSS	0.98 (0.45-2.3)	0.78	0.87 (0.35-1.8)	0.82
	UCTD	0.87 (0.32-1.8)	0.76	0.68 (0.15-0.92)	0.81
Adverse pregnancy outcomes	**Doble/triple APL positivity**	2.4 (1.24-4.2)	**0.03**	2.3 (1.1-3.9)	**0.04**
	Low C3	1.5 (1.1-3.4)	**0.04**	1.4 (1.1-3.2)	0.12
	Active disease	3.5 (2.1-5.6)	**0.002**	3.4 (1.8-5.2)	**0.004**
	Elevated ESR	1.7 (1.2-3.9)	0.06	1.5 (1.1-3.6)	0.10
	GC treatment	2.4 (1.4-4.9)	0.21	1.8 (1.2-3.4)	0.32
	Glomerulonephritis	3.1 (2.4-5.8)	**0.02**	2.4 (1.5-4.5)	0.12
	HCQ treatment	0.43 (0.14-0.89)	**0.002**	0.34 (0.05-0.72)	**0.004**
	AAS treatment	0.62 (0.32-0.92)	0.06	0.58 (0.28-0.85)	0.18
	Previous thrombosis	2.4 (1.5-5.6)	0.06	2.1 (1.2-4.9)	0.10

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