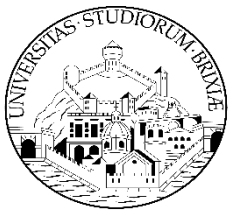

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CICLO XXXVI

SALUTE RIPRODUTTIVA NELLE PAZIENTI CON MALATTIE REUMATOLOGICHE SEGUITE PROSPETTICAMENTE DA TEAM MULTIDISCIPLINARI: ANALISI DELL'OUTCOME MATERNO-FETALE, VALUTAZIONE DELLA TERAPIA IN GRAVIDANZA E IDENTIFICAZIONE DI FATTORI DI RISCHIO PER EVENTI AVVERSI

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Abstract

Le malattie reumatologiche spesso vengono diagnosticate in donne in età fertile, le quali possono desiderare una gravidanza. Negli ultimi anni, grazie alla diagnosi precoce, alla disponibilità di terapie efficaci e alla pianificazione e gestione multidisciplinare della gravidanza, è stato possibile ottenere un miglior controllo dell'attività di malattia ed un miglioramento degli outcome materno-fetali in queste pazienti. Tuttavia, le complicanze rimangono più frequenti rispetto alla popolazione ostetrica generale.

L'influenza dell'attività di malattia sull'outcome della gravidanza e, viceversa, l'influenza della gravidanza sull'attività di malattia, così come le modifiche terapeutiche da apportare prima della gravidanza, sono solo alcuni degli aspetti che devono essere considerati in questo ambito.

Ad oggi sono ancora numerosi gli *unmet needs*, soprattutto per le pazienti con malattie rare. Inoltre, i dati disponibili in letteratura circa l'attività di malattia e la frequenza delle riacutizzazioni durante la gravidanza, la sicurezza e l'efficacia dei trattamenti anti-reumatici e l'identificazione di marker predittivi di eventi avversi, sono parziali e riguardano soprattutto alcune malattie reumatiche.

Lo scopo della presente tesi e del progetto di ricerca da cui deriva, è stato quello di esaminare il tema della salute riproduttiva su scala nazionale ed internazionale, in diverse coorti di pazienti con diagnosi di malattia reumatologica seguite durante la gravidanza da team multidisciplinari. In questo contesto, sono stati valutati gli outcome materno-fetali, l'attività di malattia e le terapie assunte durante la gravidanza in pazienti con diverse malattie reumatologiche, con l'obiettivo di identificare eventuali marker predittivi di outcome avversi. Inoltre, è stata approfondita la tematica del benessere psicologico delle pazienti con malattia reumatologica durante la gravidanza e nel post-partum.

I risultati di questa tesi hanno contribuito a una maggiore comprensione di numerosi aspetti riguardanti la salute riproduttiva nelle donne con malattie reumatologiche e hanno evidenziato l'importanza della gestione multidisciplinare e dello stretto monitoraggio della gravidanza e del post-partum in queste pazienti.

Abstract (English version)

Rheumatic diseases are often diagnosed in women of childbearing age, who may desire pregnancy. In recent years, thanks to early diagnosis, the availability of effective therapies, and pregnancy planning together with multidisciplinary management, it has been possible to achieve better control of disease activity and to improve maternal-fetal outcomes in these patients. However, complications are still more frequent compared to the general obstetric population.

The influence of disease activity on pregnancy outcomes and, conversely, the impact of pregnancy on disease activity, as well as therapeutic modifications required before pregnancy, are just some of the aspects that need to be considered in this context.

To date, there are still numerous unmet needs in this field, especially for patients with rare diseases. Indeed, available data regarding disease activity, frequency of flares during pregnancy, safety and efficacy of anti-rheumatic treatments, and predictive markers of adverse events are partial and limited to some rheumatic diseases.

The aim of this thesis and the research project from which it originates has been to investigate the topic of reproductive health on a national and international scale, evaluating different cohorts of patients diagnosed with rheumatic diseases, who were monitored during pregnancy by multidisciplinary teams. In this context, maternal-fetal outcomes, disease activity, and therapies used during pregnancy were assessed in patients with different rheumatologic diseases, with the aim also of identifying potential predictive markers of adverse outcomes. Furthermore, the issue of the psychological well-being of patients with rheumatologic diseases during pregnancy and in the postpartum period has been explored.

Overall, the results of this thesis have contributed to a better understanding of different aspects concerning reproductive health in women with rheumatic diseases and have highlighted the importance of multidisciplinary management and close monitoring during pregnancy and post-partum in these patients.

INDICE

1. Introduzione e obiettivi della tesi

Le malattie reumatologiche spesso vengono diagnosticate in donne in età fertile, le quali possono esprimere il desiderio di intraprendere una gravidanza. La salute riproduttiva in questo ambito è quindi un tema di grande importanza e implica un *management* multidisciplinare dedicato. Numerosi sono infatti gli aspetti che devono essere considerati in questo ambito e, in particolare, durante il counselling preconcezionale.

In passato la gravidanza nelle pazienti con malattia reumatologica era sconsigliata o controindicata, a causa degli outcome materno-fetali avversi che frequentemente potevano verificarsi. Negli ultimi anni la possibilità di una diagnosi precoce e la disponibilità di terapie efficaci, unitamente alla pianificazione e alla gestione multidisciplinare della gravidanza, hanno consentito un miglior controllo dell'attività di malattia e un miglioramento dell'*outcome* materno-fetale in queste pazienti. (1, 2) Tuttavia, permane un aumentato rischio di complicanze materno-fetali rispetto alla popolazione generale. (3, 4)

In generale, l'andamento della gravidanza nelle pazienti con malattia reumatologica può essere influenzato da diversi fattori.
In primo luogo, l'attività di malattia ha un impatto sull'outcome materno-fetale. In particolare, una malattia attiva prima e dopo il concepimento può comportare l'insorgenza di complicanze materno-fetali. Inoltre, in alcuni casi, la gravidanza stessa può costituire un fattore di rischio per la riacutizzazione della malattia.

In secondo luogo, si deve considerare che, mentre alcuni farmaci sono compatibili con la gravidanza e l'allattamento, altri devono essere interrotti prima del concepimento o sospesi nelle prime fasi della gravidanza, quando possibile. Questo può rendersi necessario per motivi di comprovata teratogenicità del farmaco o, in alcuni casi, per mancanza di dati relativi il loro utilizzo durante la gravidanza). (5-8)

Infine, è noto come la positività di alcuni autoanticorpi costituisca un fattore di rischio per determinate complicanze materno-fetali per cui, in questi casi, si rendono necessari monitoraggi particolari durante la gravidanza e/o terapie profilattiche aggiuntive.

Gli anticorpi anti-Ro/SSA e anti-La/SSB sono in grado di attraversare la placenta e possono causare nel neonato lo sviluppo di lupus neonatale. (9) Questa malattia autoimmune acquisita del neonato comporta, nei casi più lievi, lo sviluppo di un transitorio rash cutaneo e/o transitorio rialzo degli indici di epatolisi ma, nei casi più gravi, può comportare lo sviluppo di blocco cardiaco congenito. (10, 11) Questo si verifica nell'1-2% dei casi delle gravidanze in donne con anticorpi anti-Ro/SSA, presenta una frequenza di ricorrenza del 12-19% ed è associato ad elevata mortalità (sia in utero, che post natale: 16-28%) e morbidità (necessità di impianto pace-maker nel 70-75% dei casi). (12-15)
Nell'ambito delle malattie reumatologiche, le attuali raccomandazioni consigliano di testare gli anticorpi anti-Ro/SSA in tutte le donne con malattia reumatologica, dato che la loro positività si riscontra non solo nella Sindrome di Sjogren, per la quale costituiscono uno degli elementi classificativi, ma anche in altre malattie reumatologiche, come ad esempio nelle Connettiviti Indifferenziate (10-30%) e nel LES (30-50%). (8, 12, 16) Inoltre, questi anticorpi possono essere riscontrati anche nella popolazione generale (e in questi casi sono generalmente riscontrati dopo l'insorgenza di blocco cardiaco in un neonato da madre senza malattie reumatologiche).
Alle pazienti anti-Ro/SSA positive può essere offerto un monitoraggio ecocardiografico fetale settimanale (o bisettimanale) dalla 16° alla 26° settimana di gestazione circa, per diagnosticare precocemente l'eventuale interessamento cardiaco fetale. (2, 8) In caso di blocco cardiaco di I o II grado, si può considerare un trattamento a base di glucocorticoidi fluorinati. Considerando il basso rischio di blocco cardiaco congenito nelle donne con positività degli anticorpi anti-Ro/SSA e considerando che i risultati in letteratura riguardanti l'efficacia della terapia steroidea sono contrastanti, non è del tutto chiaro se lo stretto monitoraggio dell'ecocardiografia fetale sia da raccomandare a tutte le donne con

anticorpi anti-Ro/SSA positivi senza precedenti gravidanze complicate da questa manifestazione. Tuttavia, nella decisione, si può tener presente che generalmente le donne accettano volentieri di sottoporsi a questo monitoraggio che, peraltro, non è invasivo. (17, 18) Un'altra terapia da considerare è l'idrossiclorochina, che potrebbe ridurre il rischio di ricorrenza del blocco cardiaco congenito e di lupus neonatale cutaneo. (19-22)

Gli anticorpi anti-fosfolipidi (aPL) sono associati ad un aumentato rischio di eventi trombotici e a complicanze ostetriche. (23) L'esatto meccanismo patogenetico implicato nell'insorgenza delle complicanze ostetriche non è completamente noto. In particolare, il meccanismo trombotico non sembra essere l'unico implicato. A livello placentare, il legame degli anticorpi anti-β2glicoproteina (aβ2GPI) potrebbe attivare meccanismi infiammatori, in particolare complemento mediati, potrebbe inibire la proliferazione del trofoblasto, e avere effetti anti-angiogenetici a livello delle arterie spirali. (24) Tutti questi eventi potrebbero quindi comportare un'alterata placentazione, alla base delle morbidità ostetriche correlate alla positività di questi anticorpi. (14)
Gli anticorpi aPL vengono rilevati mediante 3 test: aβ2GPI IgG e IgM, anti-cardiolipina (aCL) IgG e IgM, e Lupus anticoagulant (LAC). A seconda del tipo, del numero di test positivi e del titolo di questi anticorpi, si possono delineare diversi profili di rischio. (25) Un profilo ad 'alto rischio' è definito dalla positività del LAC, dalla triplice positività, da titoli medio-alti di IgG e dalla persistenza della positività. (25) In caso di positività di questi anticorpi, la scelta della profilassi con basse dosi di acido acetilsalicilico associata o meno all'eparina a basso peso molecolare (EBPM) deve essere guidata dal profilo di rischio anticorpale, dall'anamnesi ostetrica e dai fattori di rischio generali (come ad esempio età materna, comorbidità, fattori di rischio cardio-vascolari). (2, 8, 25, 26)

Date queste premesse, emerge chiaramente l'importanza del counselling preconcezionale, inteso come momento in cui valutare tutti i possibili fattori di rischio associati a potenziali complicanze durante la gravidanza e discuterne con la paziente, allo scopo di stratificare il rischio, pianificare il *timing* per la

gravidanza e di definire una strategia terapeutica e di *follow-up* per minimizzare il rischio di tali complicanze. Inoltre, appare chiaro come il counselling preconcezionale e il follow-up della gravidanza debbano essere il più possibile individualizzati e si debbano avvalere di una collaborazione multidisciplinare. (14)

Nonostante gli enormi progressi in questo ambito, ad oggi sono ancora numerosi gli *unmet needs* e numerosi sono gli obiettivi da raggiungere. Infatti, ancora oggi le malattie reumatologiche possono influire sulla pianificazione familiare. Molte donne mostrano preoccupazione per l'impatto che la malattia può avere sulla cura e crescita dei loro figli e per i possibili effetti collaterali della terapia che dovranno assumere durante la gravidanza e l'allattamento. (27-29)

I dati in letteratura riguardanti l'attività di malattia e la frequenza dei *flare* durante la gravidanza, l'efficacia e la sicurezza dei farmaci anti-reumatici e l'identificazione di marcatori predittivi di eventi avversi, sono parziali. Una recente revisione della letteratura ha analizzato i dati riguardanti l'andamento delle singole malattie reumatologiche in gravidanza: la maggior parte delle casistiche riguarda gravidanze in pazienti affette da artriti infiammatorie e lupus eritematoso sistemico, mentre per altre patologie i dati sono scarsi, derivati da studi retrospettivi o *case reports*. (30-33) Inoltre, per gli stessi autori, appaiono necessari ulteriori studi prospettici dotati di una casistica più ampia ai fini di migliorare la conoscenza sull'interazione tra malattia reumatologica e gravidanza e di offrire migliori strategie terapeutiche in grado di ridurre l'attività di malattia e le complicanze durante la gravidanza. (30)

Per quanto riguarda l'utilizzo dei farmaci anti-reumatici durante la gravidanza, i dati sono ancora più limitati, in quanto derivati principalmente da *case series* e da pochi studi prospettici; inoltre, è noto che le donne in gravidanza sono escluse dai trial randomizzati controllati. (5, 34, 35) Un aiuto, in qualche caso anche significativo, è stato dato dalla raccolta degli esiti gestazionali delle pazienti uscite dai trial clinici in quanto inaspettatamente gravide, anche se questi sono ovviamente dati non sistematici e che richiedono un'importante elaborazione. Gli

studi osservazionali prospettici rappresentano quindi in questo ambito uno strumento fondamentale per verificare l'andamento delle gravidanze e l'efficacia/sicurezza delle terapie. (36) Considerando inoltre il fatto che molte malattie reumatologiche sono malattie rare, è fondamentale la collaborazione di più Centri Specialistici per riuscire ad ottenere dei dati consistenti.

Date le suddette premesse, l'obiettivo della presente tesi e del progetto di ricerca da cui deriva, è quello di approfondire l'entità del problema riproduttivo nelle pazienti con diagnosi di malattia reumatologica su scala nazionale ed internazionale; descrivere le caratteristiche clinico-laboratoristiche delle gravidanze in pazienti con malattie reumatologiche seguite in maniera prospettica; valutare l'andamento delle gravidanze nei tre trimestri, con attenzione particolare alla frequenza delle riacutizzazioni di malattia e alle terapie assunte prima, durante e dopo la gravidanza; analizzare gli outcome materno-fetali nelle diverse malattie reumatologiche e ricercare eventuali fattori di rischio per outcome avversi; approfondire la tematica della salute riproduttiva nelle pazienti con malattia reumatologica durante la gravidanza e nel post-partum.

La presente tesi riporta i risultati delle collaborazioni e delle attività svolte nel corso del mio progetto di Dottorato. I testi degli articoli pubblicati e degli abstract presentati ai congressi sono stati allegati interamente in caso di pubblicazioni *open access* ovvero riportati come abstract in caso di pubblicazioni soggette a *copyright.*

2. Capitolo 1: La salute riproduttiva e la pianificazione familiare nelle pazienti con malattia reumatologica

2.1 Introduzione e obiettivi

La salute riproduttiva nei pazienti con malattia reumatologica rappresenta un tema trasversale che comprende numerosi aspetti da tenere in considerazione.
La contraccezione, la fertilità e la pianificazione familiare sono punti di cruciale interesse nelle pazienti con malattia reumatologica, ma non sempre vengono affrontati durante la valutazione specialistica. Infatti, una recente *survey* italiana che ha incluso 398 pazienti con malattia reumatologica, ha mostrato che circa 1 donna su 3 non ha ricevuto un counselling dal proprio reumatologo di fiducia relativamente al desiderio di gravidanza né all'utilizzo di farmaci contraccettivi. Inoltre, il 36.4% delle pazienti ha affermato che la malattia reumatologica ha influenzato il numero di figli che hanno avuto o avrebbero voluto avere. (27) Questo mette in evidenza il fatto che, ad oggi, in Italia, il counselling delle donne in età riproduttiva affette da malattie reumatologiche rappresenta ancora un bisogno insoddisfatto e che quindi dovrebbe essere implementato.
Come precedentemente esposto, una consulenza preconcezionale adeguata ed esaustiva è fondamentale per effettuare una stratificazione del rischio e pianificare la gravidanza. Nei casi in cui la gravidanza si debba posticipare, a causa per esempio di malattia attiva o di assunzione di farmaci teratogeni, così come nei casi in cui la paziente non desideri una gravidanza, il tema della contraccezione diventa prioritario e deve tener conto che alcune condizioni, come la positività degli aPL, possono controindicare l'utilizzo di terapie a base di estrogeni, dato il potenziale trombotico. Invece, nei casi in cui la malattia reumatologica sia in remissione e quindi sia il momento opportuno per la ricerca di una gravidanza, è importante pianificare le eventuali modifiche terapeutiche e il *follow-up* multidisciplinare nel corso della gravidanza, per monitorare regolarmente l'attività di malattia e la progressione della gestazione. Infine, nei casi in cui il concepimento sia ritardato, e in particolare in presenza di condizioni di infertilità, un tema prioritario diventa quello del ricorso alle tecniche di

procreazione medicalmente assistita, il cui utilizzo è in aumento, che devono essere adeguatamente programmate e devono considerare, anche in questo caso, potenziali fattori di rischio che potrebbero avere un impatto negativo durante la stimolazione ovarica, come, ad esempio, l'attività di malattia e la positività degli aPL. In questo caso, la collaborazione multidisciplinare con lo Specialista Ginecologo consente di valutare il profilo di rischio della paziente in toto e di proporre, sulla base di questo, una adeguata profilassi anti-trombotica.

A livello internazionale, esistono delle linee guida e raccomandazioni dedicate al *management* degli aspetti della salute riproduttiva nelle donne con malattia reumatologica e alla compatibilità dei farmaci anti-reumatici con la gravidanza e l'allattamento. (2, 6-8) Tuttavia, i dati disponibili in letteratura sono parziali, spesso retrospettivi e derivati da piccole *case-series*, e la forza dell'evidenza correlata alle singole raccomandazioni talvolta è basata sulla *expert opinion*. Considerando inoltre che molte malattie reumatologiche sono malattie rare, gli studi prospettici e la collaborazione multicentrica sono fondamentali per meglio chiarire questi aspetti.

Al fine di migliorare e approfondire le conoscenze relative all'andamento e all'outcome delle gravidanze nelle pazienti affette da malattie reumatologiche e agli effetti delle terapie durante la gravidanza e l'allattamento, in alcuni Stati europei sono stati creati dei Registri dedicati. (37) In Italia è stato avviato il progetto P-Rheum.it, a cui partecipa l'U.O. di Reumatologia e Immunologia Clinica dell'ASST Spedali Civili di Brescia e che fa parte degli Studi Strategici della Società Italiana di Reumatologia (SIR). Esso costituisce il primo registro nazionale italiano con lo scopo di raccogliere i dati delle gravidanze (e dei bambini fino ad un anno di età) seguite prospetticamente nei Centri di Reumatologia in cui esiste un ambulatorio dedicato alle gravidanze in pazienti con malattie reumatiche.

Inoltre, In Italia, fino a poco tempo fa, non esistevano linee guida riguardanti queste tematiche. Nel luglio 2021 la SIR ha identificato come prioritaria la tematica della salute riproduttiva per la creazione di una linea guida italiana per

la pratica clinica in reumatologia e ha individuato un team per lo sviluppo di tali Linee Guida.

Il mio contributo scientifico in questo ambito è legato alla partecipazione attiva ai due progetti promossi dalla SIR: il P-Rheum.it e lo sviluppo delle linee guida italiane per la pratica clinica sulla salute riproduttiva nelle malattie reumatologiche.

Gli obiettivi di questi progetti sono stati: approfondire la tematica della salute riproduttiva nelle pazienti con diagnosi di malattia reumatologica su scala nazionale; descrivere le caratteristiche clinico-laboratoristiche delle gravidanze in pazienti seguite in maniera prospettica e valutare l'andamento delle gravidanze nei tre trimestri, con attenzione particolare alla frequenza delle riacutizzazioni di malattia e alle terapie assunte; analizzare gli outcome materno-fetali; sviluppare le prime linee guida nazionali sulla salute riproduttiva nei pazienti con malattie reumatologiche.

2.2 Risultati: implementazione del registro P-Rheum.it

Il P-Rheum.it è il registro italiano dedicato alla raccolta prospettica dei dati delle gravidanze in pazienti con malattie reumatologiche (e dei loro bambini, fino ad un anno di età). Si tratta di uno studio strategico della Società Italiana di Reumatologia a cui partecipano 30 Centri reumatologici italiani specializzati (in cui sia attivo un ambulatorio dedicato) e l'U.O. di Reumatologia e Immunologia Clinica dell'ASST Spedali Civili di Brescia vi partecipa in qualità di Centro coordinatore. Durante i tre anni del Dottorato ho avuto la possibilità di selezionare, valutare e seguire le pazienti arruolate nel Registro afferenti all'ambulatorio multidisciplinare dedicato alle gravidanze nelle pazienti con malattie autoimmuni sistemiche della U.O. di Reumatologia e Immunologia Clinica dell'ASST Spedali Civili di Brescia. Sono state incluse pazienti di età compresa tra i 18 e i 45 anni, entro la 20° settimana di gestazione, con una diagnosi di malattia reumatologica o positività confermata di autoanticorpi non

organo-specifici. Le malattie reumatologiche incluse nel registro sono: Artrite Reumatoide, Artrite Idiopatica Giovanile, Artrite Psoriasica, Spondilite Anchilosante, Spondiloartrite, Artrite Indifferenziata, Connettivite Indifferenziata, Sindrome di Sjogren, Lupus Eritematoso Sistemico, Sindrome da Anticorpi Antifosfolipidi, Sclerosi Sistemica, Vasculiti, Miositi Infiammatorie. Sono state inoltre incluse donne con positività anticorpali confermate, in particolare donne con aPL positivi o anti-Ro/SSA positivi.

Oltre alla selezione delle pazienti e all'inserimento dati, è stata effettuata, in collaborazione con il Cetro Studi della SIR, una analisi *ad interim* dei dati inseriti nel registro fino ad aprile 2021. Ai fini dell'analisi, sono state predisposte 3 tabelle, i cui *item* sono stati selezionati tra un numero elevato di variabili (più di 300) presenti nel registro. Le tabelle avevano lo scopo di descrivere:

1) le caratteristiche della popolazione, sia da un punto di vista demografico (età, etnia, stato civile, titolo di studio) che patologico (comorbidità, autoimmunità, attività di malattia al pre-concezionale e al momento dell'arruolamento);

2) l'anamnesi ostetrica delle pazienti e l'andamento della gravidanza, così come l'outcome neonatale e l'attività di malattia al post-partum;

3) le terapie assunte dalle pazienti al momento della valutazione pre-concezionale, nei tre trimestri e nel post-partum.

A novembre 2021 ho avuto la possibilità di presentare i risultati preliminari relativi a 536 gravidanze in pazienti con malattie reumatologiche durante il Congresso Nazionale della Società Italiana di Reumatologia: l'abstract è stato accettato come comunicazione orale, in lingua inglese, nella sessione 'Verso EULAR' *(*Allegato 1, tratto dalla Rivista *'Reumatismo', numero speciale per il 58° Congresso Nazionale SIR).*

Nel 2022 ho inoltre partecipato all'aggiornamento di questi dati i cui risultati sono stati presentati in occasione del Congresso EULAR 2022 *(*Allegato 2, tratto dalla Rivista *'Annals of the Rheumatic Diseases', EULAR European Congress of Rheumatology 2022, Abstracts).*

A maggio 2023 si è concluso l'arruolamento nel Registro (pur proseguendo l'inserimento dei dati delle pazienti precedentemente arruolate). Sono state arruolate in totale 1298 gravidanze. Prima di procedere con l'estrazione dei dati, sono state definite e successivamente inviate a tutti i Centri partecipanti delle *query*, per il *data cleaning*, che si è concluso in agosto 2023. Attualmente è in corso l'estrazione dei dati, in collaborazione con il Centro Studi SIR, ed è in corso la stesura del paper descrittivo, che comprenderà tutte le gravidanze inserite nel registro P-Rheum.it per cui siano disponibili i dati relativi all'esito gestazionale (n= 1018) e cha andrà a valutare aspetti epidemiologici, l'attività di malattia durante la gravidanza, le terapie assunte, l'outcome gestazionale e neonatale e il follow-up a 6 mesi.

2.3 Risultati: sviluppo delle Linee Guida per la Pratica Clinica sulla Salute Riproduttiva nelle Malattie Reumatologiche da applicarsi nel contesto della Reumatologia italiana, in collaborazione con il Centro Studi della Società Italiana di Reumatologia (SIR)

A novembre 2021 sono stata selezionata come collaboratore nel gruppo di studio metodologico per la realizzazione di una 'Linea Guida per la Pratica Clinica sulla Salute Riproduttiva nei Pazienti con Malattie Reumatologiche' promossa dalla Società Italiana di Reumatologia, in collaborazione con il Centro Studi SIR.
Il progetto aveva l'obiettivo di produrre e pubblicare le prime linee guida italiane sull'argomento, utilizzando la metodologia GRADE-ADOLOPMENT in conformità ai requisiti del Sistema Nazionale delle Linee Guida e dell'Istituto Superiore di Sanità. (38) Le recenti Linee Guida ACR (American College of Rheumatology), pubblicate nel 2020, sono state individuate come riferimento. (8)
In particolare, ho partecipato alle attività dell'*evidence review team*, gruppo di lavoro metodologico composto da altri 3 partecipanti e da 2 coordinatori. Nei primi mesi le attività svolte si sono concentrare sulla stesura del protocollo, sull'individuazione degli stakeholder (all'interno del Gruppo di Studio sulla medicina di genere della Società Italiana di Reumatologia) e sulla formulazione e prioritizzazione dei quesiti clinici. La qualità delle linee guida ACR è stata inoltre

valutata mediante *dell'Appraisal of Guidelines Research and Evaluation* (AGREE) II.

Successivamente, è stata condotta una revisione sistematica della letteratura, sui è seguito un aggiornamento a gennaio 2023. Per ciascuna pubblicazione selezionata, sono stati estratti i dati di interesse e sono stati valutati il rischio di *bias* e la qualità dell'evidenza*,* utilizzando gli strumenti: *Risk Of Bias In Non-randomised Study of Interventions* (ROBINS)-I; *Revised Cochrane risk-of-bias tool for randomized trials* (RoB2); *Quality In Prognostic Studies* (QUIPS). (39-41) Infine è stata realizzata una sintesi dell'evidenza.

Sono state poi formulate le raccomandazioni, che sono state discusse con il *panel* di esperti durante *meeting online*. Il *panel* di esperti è stato coordinato dalla Professoressa Angela Tincani ed era costituito da 18 Medici Specialisti (con esperienza in reumatologia, allergologia e immunologia clinica, medicina interna, nefrologia, ginecologia e ostetricia e neonatologia), 1 Infermiera professionale, 1 psicologa clinica e 1 rappresentate dell'Associazione Nazionale Malati Reumatici.

Al termine dei lavori con il panel, è stato redatto un documento riportante tutte le raccomandazioni discusse e le appendici tecniche. Tale documento, dopo approvazione finale del panel e revisione da parte di 3 revisori esterni, è stato sottomesso sulla piattaforma istituzionale del Sistema Nazionale Linee Guida. A settembre 2023 le prime linee guida italiane sulla salute riproduttiva nei pazienti con malattie reumatologiche sono state approvate dall'ISS e il testo completo è attualmente consultabile al sito https://www.iss.it/it/web/guest/-/salute-riproduttiva-in-pazienti-con-malattie-reumatologiche.

3. Capitolo 2: La gravidanza nelle pazienti con Lupus Eritematoso Sistemico e/o Sindrome da Anticorpi Antifosfolipidi

3.1 Introduzione e obiettivi

Il Lupus Eritematoso Sistemico (LES) è una malattia autoimmune sistemica cronica caratterizzata da un ampio spettro di manifestazioni cliniche e laboratoristiche, di entità variabile. In review pubblicata nel 2022 e che ha incluso studi pubblicati nei 5 anni precedenti, l'incidenza in Europa variava tra 1,5 e 7,4 /100000 persone/anno mentre la prevalenza variava tra 29 e 210 /100000 persone. (42) Uno studio epidemiologico italiano del 2015 ha valutato l'incidenza e la prevalenza del LES in una popolazione proveniente dalla Valtrompia; l'incidenza tra il 2009 e il 2012 è stata di 3.9/100000 abitanti mentre la prevalenza al 2012 era di 39,2/100000 abitanti. (43) Nella maggior parte dei casi, l'esordio di malattia è tra i 16 e i 55 anni, con una spiccata predilezione per il sesso femminile. In questa fascia d'età infatti il rapporto femmine:maschi varia da 7:1 a 15:1. (44-46)

Il LES quindi interessa principalmente donne in età fertile, che nel corso della loro vita possono esprimere il desiderio di maternità. In passato, la gravidanza in queste pazienti era gravata da un elevato rischio di eventi avversi materni e fetali ed era quindi frequentemente sconsigliata. È noto infatti che la gravidanza stessa può avere un impatto sull'attività di malattia e, viceversa, la malattia può avere un impatto sull'outcome materno-fetale e, per quanto l'outcome sia migliorato negli ultimi decenni, nelle pazienti con LES permane un aumentato rischio di complicanze rispetto alla popolazione ostetrica generale. (14, 47-53)

La frequenza di *flare* durante la gravidanza può variare dal 15% al 50%. (33, 54) La variabilità tra le diverse casistiche potrebbe essere legata al fatto che la definizione di *flare* varia a seconda degli studi (può infatti essere valutata mediante indici clinimetrici, mediante il *Physician Global Assessment*, oppure

definite dall'insorgenza o peggioramento di una manifestazione clinica). In questo contesto, l'attività di malattia nel periodo preconcezionale è un fattore chiave, associato ad un aumentato rischio di *flare* durante la gravidanza, che generalmente coinvolge lo stesso organo precedentemente interessato (soprattutto per quanto riguarda l'interessamento renale, cutaneo ed ematologico). Oltre che per il rischio materno, l'importanza del controllo della malattia durante la gravidanza è legata anche al fatto che l'elevata attività di malattia e i *flare* in gravidanza sono associati allo sviluppo di complicanze ostetriche, quali la pre-eclampsia/eclampsia, le perdite fetali e il parto pretermine. Durante la gravidanza, è possibile monitorare l'attività di malattia utilizzando una versione leggermente modificata dello SLEDAI (SLE *Disease Activity Index*), lo SLEPDAI (SLE-*Pregnancy Disease Activity Index*), che prende in considerazione le fisiologiche modifiche di alcuni parametri dovute alla gravidanza stessa. (55)

Per quanto riguarda l'outcome materno fetale, nelle gravidanze in pazienti con LES, la frequenza di aborto spontaneo può variare dal 10 al 25% a seconda delle casistiche. Tra i fattori di rischio indipendentemente associati alle perdite fetali sono stati riscontrati: la gravidanza non programmata, l'attività di malattia, la riduzione del C3, la proteinuria delle 24h >1g/die. (51, 53, 56)
Il parto pretermine può verificarsi nel 25-40% delle gravidanze in pazienti con LES. In genere può essere dovuto alla pPROM (*preterm Premature Rupture of Membranes*) o può essere secondario a pre-eclampsia/eclampsia ed è associato all'utilizzo di steroide, ad uno scarso controllo di attività della malattia, alla positività degli anticorpi aPL, all'interessamento renale. (51, 53, 57)
Infine, i disordini ipertensivi della gravidanza come l'ipertensione gestazionale, la pre-eclampsia, l'eclampsia e la sindrome HELLP (*Hemolysis, Elevated Liver enzymes and Low Platelets*) possono verificarsi nelle gravidanze in pazienti con LES, in particolare in presenza di interessamento renale e aPL. (58, 59) È fondamentale tenere presente che sia i fisiologici cambiamenti della gravidanza che la pre-eclampsia possono mimare alcune manifestazioni di LES; in questo contesto, il dosaggio degli anticorpi anti-dsDNA e del complemento sono uno strumento utile per la diagnosi differenziale. (2)

Una meta-analisi che ha incluso studi dal 2001 al 2016 ha mostrato come l'outcome materno nelle gravidanze in pazienti con LES fosse gravato da un rischio relativo maggiore di pre-eclampsia, ipertensione gravidica, abortività, malattia tromboembolica e infezioni post-partum. (48) Per quanto riguarda invece l'outcome fetale, vi era un aumentato rischio di parti pretermine, di neonati *small for gestational age* (SGA), di ricovero in terapia intensiva neonatale e di malformazioni congenite. (48)

Per quanto i dati in letteratura siano difformi, derivanti da casistiche non omogenee, queste complicanze sono riscontrabili nella pratica clinica quotidiana e il rischio individuale deve essere adeguatamente valutato durante il counselling preconcezionale ai fini di definire una strategia di monitoraggio durante la gravidanza. Questa, ad esempio, può includere delle valutazioni ecografiche aggiuntive nel terzo trimestre, per individuare precocemente lo sviluppo di *Intra-Uterine Growth Restriction* (IUGR), come consigliato dalle raccomandazioni EULAR (2)

In particolare, durante il counselling preconcezionale, ai fini della stratificazione del rischio, devono essere considerati sia fattori malattia-correlati che fattori di rischio generali. Le raccomandazioni EULAR riguardanti la salute della donna e il *management* del *family planning*, delle tecniche di procreazione medicalmente assistita, della gravidanza e della menopausa nelle donne con LES e Sindrome da Anticorpi Antifosfolipidi (APS) forniscono un elenco di aspetti da valutare per il counselling di queste pazienti. (2) Tra i fattori di rischio malattia-correlati riconosciuti vi sono:

- Attività di malattia nei 6-12 mesi precedenti la gravidanza, associata ad aumentato rischio di *flare* durante la gravidanza e il post-partum, di sviluppo di disordini ipertensivi e di complicanze fetali (perdite fetali, IUGR, parto pretermine);

- Anamnesi di glomerulonefrite lupica o interessamento renale attivo al concepimento, forte fattore di rischio per *flare* renale durante la gravidanza, perdite fetali e parto pretermine);
- Attività sierologica, valutata mediante la determinazione degli anti-dsDNA e delle frazioni C3 e C4 del complemento, associata ad aumentato rischio di *flare* e a perdite fetali;
- Profilo degli aPL, correlato ad aumentato rischio di outcome materno-fetale avverso, in particolare nelle pazienti che presentano titolo medi-elevati, persistenti, positività per il LAC o positività multiple (condizioni che definiscono un profilo anticorpale ad alto rischio);
- Positività degli anticorpi anti-Ro/SSA, associati allo sviluppo di lupus neonatale;
- Danno d'organo terminale.

Tra i fattori di rischio generali invece, devono essere valutati l'età materna, la presenza di comorbidità come l'ipertensione arteriosa, il diabete mellito, il sovrappeso o l'obesità, presenza di patologia tiroidea, l'abitudine tabagica, l'abuso di alcol, lo stato vaccinale. (2)

Ad oggi numerosi sforzi sono orientati verso la ricerca e la migliore definizione di biomarcatori che possano predire l'insorgenza di eventuali complicanze (*flare* e complicanze ostetriche) durante la gravidanza e quindi contribuire ad una migliore stratificazione del rischio durante il counselling preconcezionale.
In questo contesto, le componenti C3 e C4 del complemento, che sono notoriamente correlate all'attività di malattia nei pazienti con LES al di fuori della gravidanza, potrebbero rivestire un ruolo interessante.
Da un punto di vista fisiologico, è noto come il complemento sia coinvolto già nelle prime fasi della gravidanza a livello dell'interfaccia materno-fetale. (60, 61)
Inoltre, è noto come nelle gravidanze fisiologiche si assista ad un progressivo incremento delle proteine di fase acuta, compreso il complemento. (14, 62) Una eccessiva attivazione del sistema del complemento nelle prime fasi della gravidanza, e quindi un consumo del C3 e del C4 unitamente ad un minor

aumento dei suoi livelli, può associarsi all'insorgenza di alcune complicanze ostetriche, come ad esempio la pre-eclampsia, anche nella popolazione generale. (63, 64) Alcuni studi su modelli murini hanno mostrato che sia la via classica che la via alternativa del complemento possono essere coinvolte nell'insorgenza di tali complicanze in presenza di positività per aPL. (65-67) Nell'uomo, uno studio ha mostrato la presenza di C4d nelle placente di donne con aPL positivi o pre-eclampsia e di Bb in donne senza malattie autoimmuni ma con pre-eclampsia. (68) Inoltre, la presenza di C4d a livello delle placente murine e umane è stata correlata ad outcome fetali avversi nel LES e nell'APS. (69)
In una coorte prospettica di gravidanze in pazienti con LES e/o aPL positivi, l'aumento dei livelli sierici dei prodotti di attivazione del complemento era maggiore nelle gravidanze con complicanze. (70) Altri studi hanno mostrato come, nelle gravidanze in pazienti con LES e con APS, ma anche in altre patologie reumatologiche, l'attivazione del complemento potrebbe correlarsi a complicanze ostetriche. (60, 61)
Non è ad oggi chiaro se tale attivazione sia causa o conseguenza di queste complicanze, tuttavia il ruolo dell'infiammazione e del complemento è stato considerato tra i possibili fattori di patogenesi della morbidità ostetrica determinata dagli anticorpi aPL. (24) Questo, unitamente al riscontro delle sue alterazioni in caso di complicanze ostetriche nella popolazione ostetrica generale, è indicativo del fatto che il complemento potrebbe rivestire un ruolo chiave nella genesi e nel monitoraggio dello sviluppo di *flare* e complicanze ostetriche.

Un altro aspetto che deve essere considerato durante la visita preconcezionale è quello relativo alle modifiche terapeutiche. Mentre, da un lato, alcuni farmaci non sono compatibili con la gravidanza e devono quindi essere sostituiti, altri farmaci (come l'idrossiclorochina e bassi dosi di acido acetilsalicilico) sono invece raccomandati e dovrebbero quindi essere introdotti, se non già assunti dalla paziente. (2, 8)
Diversi lavori hanno mostrato come l'idrossiclorochina, farmaco fondamentale nella terapia del LES, sia in grado di ridurre lo sviluppo di *flare* durante la

gravidanza e possa presentare anche un ruolo protettivo per quanto riguarda l'insorgenza di blocco cardiaco congenito nelle pazienti con anticorpi anti-Ro/SSA positivi. (14)

Per quanto riguarda l'utilizzo di basse dosi di acido acetilsalicilico, questo trova razionale nel fatto che la pazienti con LES presentano un aumentato rischio di sviluppare disordini ipertensivi della gravidanza (in particolare, pre-eclampsia ed eclampsia). Le raccomandazioni EULAR del 2016 ne suggeriscono l'utilizzo in pazienti con LES che presentino un aumentato rischio per queste complicanze, in particolare quindi nelle pazienti con anamnesi di interessamento renale e con positività degli aPL; le più recenti linee guida ACR raccomandano in maniera condizionata di valutarne l'utilizzo in tutte le pazienti con LES e in generale con malattie reumatologiche, andando anche a considerare i fattori di rischio generali. (2, 8)

La terapia con eparina a basso peso molecolare (EBPM), in associazione a basse dosi di acido acetilsalicilico, è da valutare nelle pazienti con una diagnosi di APS o che presentino aPL positivi, dato il rischio trombotico ed ostetrico correlato a queste condizioni. (2, 8, 25, 26) La decisione di avviare o meno tale terapia e la dose da prescrivere devono essere valutate considerando l'anamnesi della paziente (pregressa trombosi; pregressi eventi ostetrici) e il profilo di rischio anticorpale e generale della paziente.

Infine, come nella popolazione ostetrica generale, dovrebbe essere consigliata una integrazione di acido folico e basse dosi di vitamina D. (2)

La scelta della terapia, in generale, deve essere guidata dal profilo di sicurezza del farmaco durante la gravidanza e deve avere l'obiettivo di mantenere la remissione durante la gravidanza, senza provocare danni fetali. Inoltre, è fondamentale condividere l'approccio terapeutico con altri specialisti (es. nefrologi, ginecologi) e con la paziente. (5)

In questo contesto, i *'point to consider'* dell'EULAR sull'utilizzo dei farmaci anti-reumatici in gravidanza, le linee guida ACR, le linee guida della *British Society for Rheumatology* e, più recentemente, le linee guida italiane promosse dalla

SIR, riassumono le caratteristiche di compatibilità dei farmaci durante la gravidanza. (5-8)
Per quanto riguarda il farmaco biologico belimumab, farmaco monoclonale anti-Blys approvato per il trattamento del LES, le raccomandazioni ad oggi ne consigliano la sospensione al test di gravidanza positivo e l'utilizzo durante la gravidanza è riservato a quei casi in cui l'attività di malattia sia elevata, in assenza di alternative terapeutiche. (6, 8) Questa indicazione deriva sostanzialmente dal fatto che, a differenza di quello che accade per altri farmaci biologici (ad esempio, i farmaci biologici anti-TNFα), attualmente i dati in letteratura relativi alla sua sicurezza durante la gravidanza sono limitati.

Nel valutare criticamente la sicurezza dei farmaci biologici durante la gravidanza, si devono considerare diversi aspetti, tra cui la struttura molecolare, l'entità del passaggio placentare, la biodisponibilità del farmaco e la sua emivita.
Fisiologicamente, il passaggio placentare attivo delle IgG, mediato dal recettore Fc fetale espresso sul trofoblasto, inizia durante il secondo trimestre e cresce progressivamente. (71, 72) I farmaci monoclonali che presentano la porzione Fc delle IgG sono quindi coinvolti in questo passaggio e l'entità del passaggio può variare a seconda della struttura molecolare. Questo comporta che, in caso di madri trattate nella seconda parte della gravidanza, il farmaco si possa riscontrare nel sangue cordonale in concentrazioni elevate e la presenza di queste molecole nella circolazione neonatale potrebbe comportare un aumentato rischio infettivo o citopenie/alterazioni nella risposta immunitaria. (71, 73)

In letteratura esistono diversi dati relativi l'utilizzo dei farmaci biologici anti-TNFα, farmaci utilizzati da più tempo per il trattamento delle artriti infiammatorie e delle malattie infiammatorie croniche intestinali, la maggior parte dei quali non ha mostrato un aumentato rischio di aborti, parti pretermine, basso peso alla nascita, malformazioni congenite, infezioni nei primi mesi di vita del neonato esposto. Attualmente questi farmaci possono essere proseguiti durante la gravidanza e le raccomandazioni consigliano timing di sospensione differenti a seconda del tipo di molecola utilizzata (in caso di malattia in remissione). (5, 6, 8, 72)

I dati relativi ad altri farmaci biologici, tra cui belimumab, invece, sono molto limitati. (71) Studi su animali hanno mostrato il passaggio transplacentare di belimumab, quando somministrato per tutta la gestazione, in assenza di anomalie congenite nella prole; la linfopenia B rilevata nella prole è stata reversibile. (74) Recentemente, il passaggio transplacentare di belimumab è stato dimostrato nell'uomo, andando a misurare i livelli di farmaco nel siero di una madre trattata fino alla 26° settimana gestazionale e del suo neonato (al momento del parto, e 4 e 7mesi dopo il parto). Il belimumab era presente nel sangue cordonale alla nascita, mentre non era più rilevabile dopo 4 mesi e, analogamente, i linfociti B del neonato erano al di sotto dei valori normali alla nascita per poi normalizzarsi dopo 4 mesi dal parto. È importante notare il fatto che la risposta vaccinale del neonato fosse normale.
Inoltre, nonostante i diversi limiti riconosciuti dagli stessi autori, una recente analisi dei dati provenienti dai trial clinici (n=110), dal *Belimumab Pregnancy Registry* (n=56) e dalle segnalazioni post-marketing/spontanee (n=137), non ha riscontrato un pattern specifico di malformazioni. (75) Tuttavia, il numero di gravidanze osservate non era sufficiente per poter raccomandare l'utilizzo di belimumab durante la gravidanza. Inoltre, la mancanza di un gruppo di controllo, i *missing data* e la presenza di fattori confondenti non hanno reso possibile trarre dei risultati conclusivi ed è stato quindi possibile fornire solo una analisi di tipo descrittivo. Sono infatti numerosi gli aspetti che devono essere considerati per poter considerare un farmaco compatibile con la gravidanza, e in ambito reumatologico si devono considerare anche ulteriori fattori, come il possibile concomitante utilizzo di farmaci teratogeni, l'attività di malattia, la positività degli anticorpi anti-Ro/SSA. (75)

Sebbene non siano ad oggi emersi elementi di preoccupazione per l'utilizzo di belimumab in gravidanza e che le linee guida contemplino il suo utilizzo in casi di malattia grave, ulteriori dati per confermarne con maggio certezza il profilo di sicurezza sono necessari. Questo appare di grande rilevanza soprattutto se si considera l'impatto che la sospensione del belimumab potrebbe avere sull'attività

di malattia. Infatti, la sospensione della terapia al test di gravidanza positivo potrebbe comportare una riacutizzazione di malattia durante la gravidanza (già di per sé periodo a rischio) e portare alle correlate complicanze ostetriche. Appare quindi prioritario identificare dei fattori che permettano di stratificare il rischio al momento della valutazione preconcezionale per poter avere più elementi nella valutazione del rapporto rischio-beneficio tra la sospensione della terapia e la sua prosecuzione durante la gravidanza, ai fini di consentire un ottimale controllo della malattia e prevenirne una riacutizzazione.

Date le suddette premesse, gli obiettivi e le mie attività in questo ambito si sono concentrati sulla ricerca di marcatori predittivi di complicanze, con particolare attenzione al ruolo del complemento, e alla valutazione dell'effetto di alcune terapie sull'attività di malattia in gravidanza e sugli outcome in relazione all'utilizzo di alcune terapie.

3.2 Risultati: il ruolo del complemento nelle gravidanze in pazienti con Lupus Eritematoso Sistemico

Al fine di approfondire il ruolo del complemento come possibile biomarcatore di complicanze materno-fetali nelle gravidanze in pazienti con LES, è stata valutata la variazione dei livelli di complemento durante la gravidanza in relazione ai *flare* e all'outcome ostetrico in una coorte bi-centrica. Alla raccolta dei dati e alla preliminare analisi, avvenuta tra il 2018 e il 2020 e oggetto della mia tesi di Specialità, è seguita una più approfondita analisi statistica e la successiva stesura del manoscritto, recentemente pubblicato sulla rivisita 'The Journal of Rheumatology' (Allegato 3, Abstract), accompagnato da un Editoriale dedicato. (76, 77) Inoltre, i risultati preliminari erano stati presentati come poster durante il Congresso EULAR 2021 (Allegato 4, *tratto dalla Rivista 'Annals of the Rheumatic Diseases', EULAR European Congress of Rheumatology 2021, Abstracts)* e come comunicazione orale al Congresso Rheumapreg 2021.

Sono state incluse 172 pazienti con LES per un totale di 246 gravidanze seguite prospetticamente presso gli ambulatori multidisciplinari dedicati alla gravidanza nelle pazienti con malattie autoimmuni sistemiche dell'Unità Operativa di Reumatologia e Immunologia Clinica dell'ASST Spedali Civili di Brescia e dell'Unità di Reumatologia di Pisa, dal 1987 al 2018. I livelli e la variazione del C3 e del C4 nelle pazienti con LES (stratificati in base allo sviluppo di *flare* in gravidanze e in base allo sviluppo di complicanze ostetriche) sono stati valutati al preconcezionale e nei tre trimestri, e confrontati con quelli della popolazione ostetrica generale. Inoltre, per determinare la riduzione o meno del complemento durante la gravidanza, sono stati utilizzati dei *cut-off* precedentemente calcolati sulla popolazione ostetrica generale. (62)

I *flare* sono stati registrati in 30 gravidanze (12%) mentre le complicanze ostetriche (suddivise in: aborti precoci e tardivi, parto pretermine severo e disordini ipertensivi della gravidanza) sono avvenute in 47 gravidanza (19%).

In generale, i livelli di C3 e di C4 si sono mostrati più elevati nella popolazione ostetrica generale rispetto alle gravidanze con LES, anche rispetto alle gravidanze LES non complicate da *flare* o da complicanze ostetriche.

Nelle gravidanze della popolazione ostetrica generale e nelle gravidanze LES senza complicanze, i livelli di C3 e di C4 aumentavano progressivamente in maniera simile nei due gruppi. Questo incremento non era presente nel gruppo di gravidanze con *flare* o nel gruppo di gravidanze con complicanze ostetriche.

In analisi multivariata, la presenza di consumo del C4 al preconcezionale ma, da notare, non l'attività di malattia calcolata nello stesso periodo mediante SLEDAI, si è mostrato fattore indipendente per lo sviluppo di *flare* durante la gravidanza.

Per approfondire il ruolo del complemento come biomarcatore predittivo di eventi avversi nelle gravidanze LES, è stata ideata e sviluppata una *network* meta-analisi, in collaborazione con i colleghi dell'Università di Torino e dell'Università di Milano.

Come prima cosa, sono state identificate le pubblicazioni relative alle gravidanze in pazienti con LES. I criteri di inclusione sono stati: natura prospettica dello studio; numerosità delle gravidanze maggiore di 50; esclusione degli aborti

precoci (<12° settimana gestazionale). Inizialmente sono stati selezionati 19 articoli e sono stati contattati gli autori chiedendo di compilare un database creato *ad hoc* per raccogliere le informazioni sul complemento e altre informazioni non presentate nei lavori. Per la creazione del database, sono state selezionate alcune variabili note per il loro impatto sull'outcome materno-fetale nelle pazienti con LES: gravidanza programmata, anamnesi di glomerulonefrite lupica, positività degli aPL, APS, terapia con basse dosi di acido acetilsalicilico, terapia con eparina a basso peso molecolare e combinazione delle due durante la gravidanza, riacutizzazioni durante la gravidanza. Per ciascun gruppo sono stati richiesti i valori medi di C3 e di C4 6 mesi prima del concepimento, al concepimento, nei tre trimestri e 3 mesi dopo il parto. Sono stati inoltre richiesti gli outcome ostetrici, definiti come: aborto >12° settimana di gestazione, morte neonatale dovuta a prematurità o a insufficienza placentare, parto pretermine <36° settimana gestazionale dovuto a ipertensione gestazionale, pre-eclampsia o insufficienza placentare.

In 15 casi, i dati richiesti non erano disponibili o gli autori non hanno risposto all'email. Sono quindi stati inclusi nell'analisi 4 lavori, per un totale di 532 pazienti con LES.

I livelli di C3 e di C4 si sono mostrati inferiori nelle gravidanze che hanno avuto un *flare* (n=170, 32%), in tutti i *timepoint* considerati, rispetto alle gravidanze senza *flare*. Considerando le gravidanze in pazienti con interessamento renale (n= 237, 44,5%), i livelli di C3 e di C4 sono risultati superiori, rispetto al gruppo senza interessamento renale, al momento del concepimento ma diventavano inferiori rispetto al gruppo di controllo già nel primo trimestre. Inoltre, la riduzione o il mancato incremento dei livelli di C3 e di C4 tra il primo trimestre e il concepimento (ΔC3 e ΔC4), si è mostrata associata allo sviluppo di *flare* durante la gravidanza.

I risultati di questa *network* meta-analisi sono stati presentati a Congressi Internazionali quali l'EULAR Congress 2022 (Allegato 5, tratto dalla Rivista *'Annals of the Rheumatic Diseases', EULAR European Congress of Rheumatology 2022, Abstracts*) e il 13th *European Lupus Meeting* 2022;

recentemente il lavoro è stato accettato dalla rivista *'Autoimmunity Reviews'* ed è in fase di pubblicazione (Allegato 6, *Journal pre-proof*).

Ai fini di validare e consolidare i risultati ottenuti, è stato organizzato uno studio prospettico multicentrico, che è stato proposto in occasione della riunione dell'*EULAR Study Group on Reproductive Health and Family Planning* tenutasi in occasione del congresso EULAR 2023.

3.3 Risultati: il ruolo del complemento nelle gravidanze in pazienti con Sindrome da Anticorpi Antifosfolipidi o positività degli anticorpi anti-fosfolipidi

Nell'ambito del presente progetto, ho avuto la possibilità di contribuire ad uno studio retrospettivo multicentrico che aveva lo scopo di approfondire il ruolo prognostico dei livelli preconcezionali di C3 e di C4 sull'outcome delle gravidanze pazienti con APS o in donne con positività degli aPL. Sono state raccolte le informazioni demografiche, i dati clinico-laboratoristici e l'outcome delle gravidanze in questa categoria di pazienti. Gli outcome avversi considerati sono stati: aborto spontaneo precoce (<10° settimana di gestazione), aborto spontaneo tardivo (>10° settimana di gestazione), morte neonatale (entro il 28° giorno di vita), parto pretermine (<37° settimana gestazionale), pre-eclampsia, eclampsia, sindrome HELLP.
Sono state incluse 260 gravidanze in 197 pazienti (76 aPL *carriers*, 184 APS).
Per quanto riguarda il profilo anticorpale, 62 gravidanze (23,8%) presentavano triplice positività, 55 (21,2%) presentavano duplice positività e 143 (55%) presentavano singola positività; il LAC era presente in 97 gravidanze (37,3%).
In 115 casi (44,2%) è stato riportato un outcome avverso; in queste gravidanze, i livelli di complemento (sia C3 che C4) al preconcezionale erano inferiori rispetto a quelli misurati nelle gravidanze senza complicanze. Inoltre, una maggiore frequenza di aborti e morti neonatali e di parti pretermine è stata osservata nelle gravidanze in pazienti che al preconcezionale presentavano bassi livelli di C3 e/o C4, rispetto alle gravidanze in cui il complemento era normale. In analisi

multivariata, la triplice positività era l'unico fattore indipendentemente associato alla presenza di complicanze durante la gravidanza, mentre il complemento o la diagnosi di APS non lo erano. Andando a valutare questo sottogruppo di gravidanze, è stato osservato come il complemento fosse ridotto al preconcezionale nel 77,4% dei casi; inoltre, in questo gruppo di gravidanze (ma non nel gruppo di gravidanze in pazienti con singola o doppia positività) la presenza di complemento riotto al preconcezionale era associata alle perdite fetali e morti neonatali. Infine, andando a valutare la terapia, è emerso che nelle pazienti con triplice positività e consumo del complemento trattate con idrossiclorochina in aggiunta alla terapia standard vi fosse una percentuale di complicanze inferiore rispetto alle pazienti con le stesse caratteristiche laboratoristiche ma non trattata con idrossiclorochina.
I risultati completi sono stati pubblicati sulla rivista '*Biomedicines*' (Allegato 7).

3.4 Risultati: il ruolo dell'attività di malattia e dell'utilizzo di basse dosi di acido acetilsalicilico nelle gravidanze in pazienti con Lupus Eritematoso Sistemico

Come precedentemente riportato, è noto come l'attività di malattia sia un fattore determinante per l'*outcome* delle gravidanze in pazienti con LES. Per approfondire quale sia il *target* ideale a cui aspirare nelle pazienti con LES che desiderano una gravidanza e, nello specifico, per valutare l'impatto dello stato di remissione o di bassa attività di malattia sull'*outcome* materno-fetale, ho partecipato ad uno studio retrospettivo multicentrico, i cui risultati sono stati pubblicati nel 2021 sulla rivista '*Rheumatology*' (Allegato 8).

In sintesi, sono stati raccolti i dati delle gravidanze in pazienti con LES seguite prospetticamente in 4 *pregnancy clinic*, con particolare attenzione sulla attività di malattia e in particolare su:

- remissione, definita dal *Definition of Remission in SLE* (DORIS), con suddivisione dei pazienti sulla base di: remissione clinica in trattamento,

remissione clinica senza trattamento, remissione completa in trattamento, remissione completa senza trattamento;

- bassa attività di malattia, come definita dal *Lupus Low Disease Activity State* (LLDAS).

Sono state incluse nell'analisi 347 gravidanze in 281 pazienti con diagnosi di LES. Le gravidanze esitate in aborto precoce (n=43) sono state escluse dall'analisi principale.

Nel 24% delle gravidanze si è verificato un *flare* durante la gravidanza o nel post-partum. Questo gruppo presentava una durata di malattia inferiore, una maggiore frequenza di interessamento renale, e livelli di C3 e C4 più bassi al baseline, rispetto al gruppo senza *flare*. Tra le gravidanze senza *flare* è stata riscontrata una maggiore frequenza di LLDAS e di remissione (sia clinica che completa) durante la prima visita in gravidanza, rispetto alle gravidanze con *flare,* ed una maggiore percentuale di trattamento con idrossiclorochina.

Nel 34,5% delle gravidanze è stato registrato un outcome avverso (morte fetale endouterine >12° settimana gestazionale; parto pretermine <37° settimana gestazionale; pre-eclampsia; IUGR; neonato SGA). Le gravidanze senza complicanze presentavano più frequentemente una LLDAS e una remissione completa, rispetto alle gravidanze esitate in outcome avverso.

In analisi multivariata, la remissione (sia clinica che completa) si è mostrata essere un fattore protettivo per lo sviluppo di *flare* mentre la sola remissione completa ha mostrato una tendenza ad essere associata ad un minor rischio di outcome avverso.

Questa collaborazione multicentrica ha posto le basi per un successivo lavoro, volto ad approfondire il ruolo protettivo dell'utilizzo di basse dosi di acido acetilsalicilico nelle gravidanze in un gruppo selezionato di pazienti con LES. I risultati sono stati pubblicati sulla rivista '*Lupus Science and Medicine*' (Allegato 9).

In sintesi, sono state incluse 216 gravidanze in 187 pazienti con LES senza anamnesi di interessamento renale e con aPL negativi, seguite in 7 centri

reumatologici europei. L'outcome composito per gli outcome ostetrici avversi comprendeva: pre-eclampsia, neonato SGA, baso peso alla nascita, IUGR, morte endouterina fetale); le gravidanze esitate in aborto precoce non sono state incluse.
Dal confronto tra il gruppo di gravidanze trattate con basse dosi di acido acetilsalicilico (n=82) e non (n=134), non sono emerse differenze nella frequenza di *flare* né nella frequenza di outcome avversi. Tuttavia è stata osservata una minor frequenza, seppur non significativa, di pre-eclampsia nel gruppo trattato.

3.5 Risultati: il ruolo del Belimumab nelle gravidanze in pazienti con Lupus Eritematoso Sistemico

Per ottenere maggiori informazioni riguardanti l'utilizzo di belimumab durante la gravidanza nelle pazienti con LES, è in corso un progetto che prevede la raccolta retrospettiva dei dati delle gravidanze in pazienti con LES trattate con belimumab. Il database anonimo, creato *ad hoc*, prevede l'inserimento di dati demografici, clinico-laboratoristici, terapie assunte nel preconcezionale, durante la gravidanza e nel post-partum, informazioni relative al *timing* di sospensione del belimumab, dati relativi all'attività di malattia nel preconcezionale e nei tre trimestri, outcome ostetrico, dati dei neonati.

Inizialmente il progetto vedeva la collaborazione di 3 Centri reumatologici italiani ma successivamente, in occasione del Congresso SIR del 2021, ho avuto modo di proporlo nell'ambito del Gruppo di Studio della Medicina di Genere della SIR e ad oggi 7 Centri reumatologici italiani hanno contribuito all'invio dei dati.

I dati relativi alle prime gravidanze inserite nel database sono stati presentati nel 2021 come poster al congresso EULAR (Allegato 10, tratto dalla Rivista *'Annals of the Rheumatic Diseases', EULAR European Congress of Rheumatology 2021, Abstracts*) e come comunicazione orale al Congresso Internazionale Rheumapreg e al Congresso Internazionale sul Lupus Eritematoso Sistemico (Lupus and CORA 2021).

Un aggiornamento della casistica, con l'inclusione di 20 gravidanze, è stato presentato come poster al Congresso dell'American College of Rheumatology (ACR Convergence) nel 2022 (Allegato 11).

Ad oggi sono stati raccolti i dati di 25 gravidanze (di cui una è stata esclusa dalla analisi per mancanza dei dati relativi all'outcome).
Al concepimento, l'età mediana delle pazienti era di 33 (range interquartile: 21-37,3) anni e la durata di malattia era 11,5 (6-16) anni. In 4 casi la gravidanza è stata ottenuta mediante tecniche di procreazione medicalmente assistita.
Durante la gravidanza, 22/24 (92%) pazienti hanno assunto steroide, 20/24 (83%) idrossiclorochina, 17/24 (71%) *conventional systemic Disease Modifying Anti-Rheumatic Drugs* (csDMARDs). In un caso, il concepimento è avvenuto dopo 15 giorni dalla sospensione del micofenolato mofetile (farmaco teratogeno). Basse dosi di acido acetilsalicilico sono state prescritte in 21/24 casi (87,5%), e in 14 casi (58%) è stata prescritta terapia con eparina a basso peso molecolare.

Belimumab è stato sospeso in 4 casi prima del concepimento, in 10 casi al test di gravidanza positivo e in 10 casi durante la gravidanza (4 nel 1° trimestre, 3 nel 2° trimestre e 3 nel 3° trimestre). In tutti i casi, l'utilizzo di belimumab durante la gravidanza è stato discusso con la paziente.

La tabella 1 riporta le caratteristiche di malattia delle pazienti, suddivise in gruppi in base al timing di sospensione del belimumab.

Tabella 1. Caratteristiche di malattia nei 3 gruppi di pazienti definiti in base del timing di sospensione della terapia con belimumab

	Pre-Concezionale (n=4)	**Test gravidanza positivo (n=10)**	**Durante la gravidanza (n=10)**
Interessamento renale	1/4 (25%)	5/10 (50%)	6/10 (60%)

Interessamento muco-cutaneo	3/4 (75%)	10/10 (100%)	10/10 (100%)
Interessamento articolare	4/4 (100%)	10/10 (100%)	8/10 (80%)
Interessamento neurologico	0/4	3/10 (30%)	1/10 (10%)
Interessamento ematologico	2/4 (50%)	7/10 (70%)	7/10 (70%)
Interessamento sierositico	2/4 (50%)	6/10 (60%)	3/10 (30%)
aPL +	2/4 (50%)	2/10 (20%)	5/10 (50%)
Singola positività aPL	0/4	1/10 (10%)	1/10 (10%)
Duplice positività aPL	2/4 (50%)	0/10	3/10 (30%)
Triplice positività aPL	0/4	1/10 (10%)	1/10 (10%)
APS	1/4 (25%)	1/10 (10%)	2/10 (20%)

Alla visita preconcezionale, l'attività mediana di malattia misurata mediante SLEDAI era di 4 (2-4).

Durante la gravidanza si sono registrati *flare* in 4 casi. Tre *flare* (uno cutaneo, uno pericarditico e uno ematologico) si sono verificati durante il 3° trimestre nel gruppo di pazienti che aveva sospeso il belimumab al test di gravidanza positivo; questi flare sono stati trattati con aumento della terapia steroidea per os a 10mg/die in tutti i casi, boli di metilprednisolone in 2 casi e aumento della posologia di ciclosporina in un caso.

Un *flare* (cutaneo ed articolare) si è verificato nel 1° trimestre in una paziente che ha proseguito il belimumab durante la gravidanza, ed è stato trattato con l'aumento dello steroide per os e una terapia topica.

Una paziente ha inoltre presentato malattia renale attiva durante tutta la gravidanza; la gravidanza era stata sconsigliata ma la paziente aveva sospeso autonomamente la terapia con micofenolato mofetile 15 giorni prima del concepimento; durante la gravidanza il micofenolato mofetile è stato sostituito dall'azatioprina e il belimumab è stato interrotto alla 11° settimana di gestazione. La paziente ha inoltre ricevuto terapia steroidea a basso dosaggio (5 mg/die) nei primi due trimestri di gravidanza.

In generale, l'outcome è stato positivo nella maggior parte dei casi, con una percentuale di nati vivi pari a 87,5%. In 6 casi il parto è stato pretermine (< 34° settimana gestazionale in un caso).
Si sono verificati 3 aborti: 2 nel gruppo di pazienti in cui il belimumab era stato sospeso prima del concepimento, rispettivamente alla 7° e 11° settimana gestazionale e 1 morte endouterina fetale in una paziente che aveva sospeso il belimumab nel 3° trimestre. In questo caso, l'aborto è stato attribuito alla presenza di un difetto atrio-ventricolare completo in un feto con trisomia 21.
Inoltre, è stata registrata una morte perinatale.

Si sono verificati 2 episodi di pre-eclampsia, in due pazienti in cui il belimumab era stato sospeso durante la gravidanza. Entrambe le pazienti presentavano dei fattori di rischio: una paziente aveva in anamnesi un interessamento renale, aveva una duplice positività per gli aPL e ha avuto una malattia renale attiva dal preconcezionale e per tutta la gravidanza; l'altra paziente presentava invece diversi fattori di rischio quali ipertensione arteriosa, abitudine tabagica e obesità e aveva una storia di pre-eclampsia insorta in una precedente gravidanza.
È stato inoltre registrato un episodio di eclampsia alla 25° con emorragia cerebrale in una paziente con anamnesi di interessamento renale e diagnosi di APS secondaria (sia ostetrica che trombotica) che era stata sottoposta a tecniche di procreazione medicalmente assistita (eterologa); la gravidanza è esitata nella morte perinatale del neonato.

Dopo la nascita, 5 dei 21 neonati sono stati ricoverati in terapia intensiva neonatale. Le cause sono state: anemia severa e vomito (dovute ad intolleranza alle proteine del latte) ed episodi di desaturazione durante l'allattamento, in neonati di due pazienti che avevano sospeso belimumab al test di gravidanza positivo; prematurità (in due casi) e distress respiratorio in nato pretermine, in neonati di 3 pazienti che avevano sospeso belimumab durante la gravidanza.
Inoltre, un neonato presentava un difetto interatriale e un situs inversus legato ad inversione del cromosoma 10 paterno.
A due mesi dalla nascita, un neonato che presentava una dilatazione calico-pielica ha sviluppato una sepsi da verosimile infezione delle vie urinarie.

Le madri hanno allattato al seno in 18/20 (90%), in 3 casi durante la terapia con belimumab.

4. Capitolo 3: La gravidanza nelle pazienti con Artrite Reumatoide e Spondiloentesoartrite

4.1 Introduzione e obiettivi

La possibilità di riacutizzazione di malattia durante la gravidanza e il post-partum nelle pazienti con artriti infiammatorie pone in primo piano la problematica della gestione della terapia al momento del counselling preconcezionale, in particolare sul *timing* di sospensione o modifica dei farmaci biotecnologici.

In passato si riteneva che la gravidanza comportasse un miglioramento dell'attività di malattia nelle pazienti affette da Artrite Reumatoide (AR) e alcuni studi retrospettivi negli anni '90 hanno riportato un miglioramento della malattia fino al 90% dei casi. Negli ultimi anni, invece, è sempre maggiore la consapevolezza che, anche nelle pazienti con AR, vi possa essere un aumentato rischio riacutizzazione di malattia durante la gravidanza, correlato con lo sviluppo di complicanze ostetriche. (78)
Nel 2018 una revisione sistematica della letteratura con meta-analisi in cui sono state incluse 204 gravidanze in pazienti con AR, ha mostrato come l'attività di malattia migliorasse in media nel 60% dei casi, con una variabilità tra gli studi che andava dal 40% al 90%. Tale percentuale era maggiore se si andavano a considerare gli studi pubblicati tra il 1983 e il 2005 (77%) rispetto a quelli pubblicati tra il 2008 e il 2016 (55,3%). Questa variabilità, secondo gli stessi autori, potrebbe essere dovuta al fatto che la disponibilità di un maggior numero di terapie efficaci nel controllo dell'attività di malattia negli ultimi anni abbia contributo al più frequente raggiungimento della remissione (o di una bassa attività di malattia) prima della gravidanza, andando quindi a ridurre il miglioramento dell'attività di malattia osservato durante la gravidanza. (31) Si deve tuttavia considerare che gli studi inclusi presentavano grande variabilità per quanto riguardava la definizione di *flare* o di miglioramento dell'attività di malattia così come negli indici utilizzati per la loro determinazione.

In generale, oltre a questi aspetti, si dovrebbe considerare anche il fatto che, probabilmente, in passato solo donne con un fenotipo di malattia meno severo desideravano e riuscivano ad ottenere una gravidanza. Oggi, infatti, la disponibilità di numerose terapie rende possibile ottenere un buon controllo di malattia anche nelle forme più severe, che in passato sarebbero state difficilmente controllabili. A questo, però, si deve aggiungere il fatto che alcune di queste terapie devono essere sospese prima del concepimento o al test positivo, in quanto non compatibili o per mancanza di dati relativi il loro utilizzo durante la gravidanza. La sospensione quindi di una terapia efficace, potrebbe comportare la riacutizzazione durante la gravidanza. (32, 79) In una coorte di 490 gravidanze in donne con AR o Artrite Idiopatica Giovanile, che presentavano nella maggior parte dei casi una bassa attività di malattia all'inizio della gravidanza, la sospensione dell'anti-TNFα entro la 20° settimana di gestazione non aveva comportato una più frequente riacutizzazione di malattia (valutata mediante *patient reported outcome*) rispetto alle pazienti che avevano proseguito la terapia oltre la 20° settimana gestazionale. (80)

Per questi motivi è fondamentale, durante il counselling preconcezionale delle pazienti con AR, valutare l'attività di malattia ed ottimizzare la terapia, ai fini di mantenere un buon controllo anche durante la gravidanza ed il post-partum. Infatti, un altro dato che emerge dalla meta-analisi, è l'osservazione di un aumento dell'attività di malattia nel post-partum nel 46,7% dei casi, per quanto i periodi post-partum presi in considerazione nei diversi studi fossero molto variabili (da 6 settimane a 6 mesi). (31)

Oltre che per l'impatto sulla qualità di vita della paziente, l'attività di malattia durante la gravidanza e l'infiammazione sistemica, così come la necessità di utilizzare terapia steroidea per controllare l'attività di malattia, potrebbero associarsi a complicanze ostetriche. (81-84)

Una recente meta-analisi ha mostrato come le pazienti con AR presentino un rischio maggiore di sviluppare pre-eclampsia, diabete gestazionale e di aborto spontaneo rispetto alla popolazione senza AR. (85) Inoltre, è stato osservato un

aumentato rischio di parto pretermine nelle pazienti con attività di malattia moderata-severa (DAS28>3,2). (85)

Negli ultimi anni si è assistito ad un progressivo interesse nello studio della salute riproduttiva nelle donne con Spondiloentesoartrite (SpA). Nella definizione di Spondiloartriti rientrano un gruppo di malattie infiammatorie che possono coinvolgere sia il rachide (sacro-ileite, spondilite) che le articolazioni periferiche (artrite, entesite, dattilite) e sono accompagnate da diversi sintomi extra-articolari (psoriasi, uveiti, malatite infiammatorie croniche intestinali). In questo gruppo rientrano quindi diverse entità nosologiche quali la spondilite anchilosante, l'artrite psoriasica (PsA), le artriti reattive e le artriti enteropatiche. (86) Nella pratica clinica, anche considerando l'assenza di marker specifici, la classificazione delle SpA può risultare difficoltosa e talvolta alcune situazioni che non rientrano nei criteri classificativi delle singole entità vengono classificate come SpA indifferenziate. (87) Data la grande variabilità delle manifestazioni associate, un differente approccio classificativo è quello proposto dal gruppo *Assessment of SpondyloArthritis* (ASAS) che prevede distinzione a seconda dell'interessamento articolare predominante, assiale (axial-Spa, axSpA) o periferico (peripheral-SpA). (88, 89) La axSpA, a sua volta, può essere suddivisa a seconda della presenza o meno sacro-ileite a livello radiologico in due gruppi: *radiographic* axSpa (r-axSpA, che corrisponde alla spondilite anchilosante) e *non radiographic* axSpA (nr-axSpA).

In generale, l'età di esordio della malattia è tra i 20-30 anni di età, interessando quindi soggetti in età fertile. Tuttavia, in passato, il tema della gravidanza in queste pazienti non era stato molto esplorato in letteratura. Questo potrebbe essere dovuto al fatto che in passato la r-axSpA (o Spondilite Anchilosante) fosse diagnosticata più frequentemente nei soggetti di sesso maschile, con un rapporto maschi-femmine fino a 10:1; studi successivi hanno mostrato come il rapporto fosse inferiore, fino ad uno studio in cui il rapporto maschi:femmine è risultato essere pari a 1,03:1. (90) La nr-axSpA, invece, sembra essere diagnosticata più frequentemente nel sesso femminile. (91)

L'attività di malattia e l'outcome della gravidanza nelle pazienti con axSpA e PsA sono stati descritti in alcuni lavori e in alcuni casi è stato riportato un peggioramento dell'attività di malattia durante la gravidanza, in particolare nel secondo trimestre, e nel post-partum. (32, 92) In alcune coorti, la sospensione della terapia con farmaci biologici all'inizio della gravidanza era associata ad un peggioramento dell'attività di malattia durante la gravidanza mentre la sua prosecuzione era associata ad una minore attività di malattia. (32, 92, 93) Inoltre, alcuni studi hanno riportato una associazione tra attività di malattia e terapia steroidea con l'outcome ostetrico. (84, 94)
Infine, in questo contesto, è importante considerare che anche nelle donne della popolazione ostetrica generale si può assistere ad un peggioramento funzionale, legato ai fisiologici cambiamenti dovuti alla gravidanza stessa e spesso, la diagnosi differenziale può risultare difficile. (95, 96)

Una recente revisione sistematica della letteratura con meta-analisi ha indagato l'attività di malattia e l'outcome ostetrico nelle gravidanze in pazienti con SpA a PsA. (97) Per quanto riguarda l'attività di malattia, sono stati inclusi 12 studi in axSpA e 7 studi in PsA. Un peggioramento nell'attività di malattia durante la gravidanza è stato descritto fino al 61,5% dei casi nelle pazienti con axSpa e tra il 15% e il 22% dei casi nei pazienti con PsA. Durante il post-partum, l'attività di malattia è peggiorata nel 22%-92% dei casi nelle pazienti con axSpA e nel 21-100% dei casi nei pazienti con PsA. (97)
La meta-analisi, che ha incluso 3 studi riguardanti la PsA e 6 studi riguardanti la SpA, ha mostrato come in queste pazienti vi sia un aumentato rischio di parto pretermine e di taglio cesareo. Nelle axSpA, inoltre, è stato osservato un aumentato rischio per neonato SGA e pre-eclampsia. (97)

Durante il counselling preconcezionale nelle pazienti con artriti infiammatorie appare quindi cruciale valutare l'attività di malattia e valutare le modifiche terapeutiche in previsione della gravidanza. Data la grande variabilità all'interno di questo gruppo di patologie, appare prioritario identificare i fattori di rischio

associati a riacutizzazione di malattia durante la gravidanza e ad outcome avverso.
Ai fini di meglio definire questi aspetti, sono state valutate due coorti di pazienti affetti da AR e SpA.

4.2 Risultati: valutazione dell'attività di malattia in relazione alle terapie assunte durante la gravidanza in pazienti con Artrite Reumatoide

Allo scopo di valutare l'attività di malattia e gli outcome ostetrici in relazione alla terapia assunta nelle pazienti con AR, nonché per ricercare eventuali fattori predittivi di complicanze, sono stati raccolti e analizzati i dati delle pazienti con diagnosi di AR che sono state seguite durante la gravidanza presso l'ambulatorio delle malattie autoimmuni sistemiche in gravidanza dell'U.O. di Reumatologia e Immunologia Clinica dell'ASST Spedali Civili di Brescia. I *timepoint* considerati sono stati: la valutazione preconcezionale, le valutazioni nei 3 trimestri di gravidanza e la valutazione post-partum. Sono state incluse nell'analisi 73 gravidanze, dopo aver escluso 9 gravidanze esitate in aborto e 1 gravidanza extra-uterina. Nel 37% delle gravidanze è stato registrato almeno un *flare* durante la gestazione. Il gruppo di gravidanze che ha sviluppato un *flare* (n=27) presentava più frequentemente, rispetto al gruppo senza *flare* (n=46): Proteina C Reattiva (PCR) elevata e malattia attiva nel primo trimestre; utilizzo di più di un bDMARD prima della gravidanza; sospensione del bDMARD al test di gravidanza positivo. In analisi multivariata, l'attività di malattia nel primo trimestre si è mostrata fattore di rischio indipendente per *flare*. Per quanto riguarda l'outcome ostetrico sono stati registrati 8 parti pretermine (11%), 12 *Premature Rupture of Membranes* (PROM) (16%), 10 neonati SGA (14%). Le gravidanze esitate in parto pretermine presentavano livelli maggiori di PCR e più elevata attività di malattia nel primo trimestre rispetto alle gravidanze a termine.
I risultati completi di questo studio sono stati pubblicati sulla rivista '*Frontiers in Pharmacology*' (Allegato 12).

4.3 Risultati: valutazione dell'attività di malattia e ricerca di fattori di rischio per flare durante la gravidanza in pazienti con Spondiloentesoartrite

Ai fini di approfondire la frequenza delle riacutizzazioni dell'attività di malattia durante la gravidanza nelle pazienti con diagnosi di SpA e di valutarne l'eventuale correlazione con la sospensione dei farmaci biotecnologici, nonché ricercare fattori di rischio predittivi di riacutizzazione di malattia, sono stati raccolti retrospettivamente e analizzati i dati delle gravidanze seguite presso due Centri reumatologici: U.O. Reumatologia e Immunologia Clinica dell'ASST Spedali Civili di Brescia e *Serviço de Reumatologia e Doenças Ósseas Metabólicas dell'Hospital de Santa Maria* di Lisbona.
Sono state incluse 122 gravidanze (53 PsA, 39 axSpA, 6 SpA enteropatiche, 4 artriti reattive e 20 SpA indifferenziate) in 106 pazienti, seguite prospetticamente tra il 2009 e il 2021.
Ai fini dell'analisi dell'attività di malattia durante la gravidanza, sono state escluse 16 gravidanze esitate in aborto. Nel 40% delle gravidanze è stato registrato almeno un *flare* di malattia durante la gravidanza, più frequentemente nel secondo trimestre (1° trimestre: 13 flare; 2° trimestre: 24 flare; 3° trimestre: 12 flare). Anche nel post-partum si è verificato un flare nel 40% dei casi. La frequenza dei *flare* non è apparsa differente nel gruppo di gravidanze in pazienti con diagnosi di PsA rispetto al gruppo con le altre diagnosi. Nel gruppo di gravidanze con *flare* è stato osservato una maggior frequenza di interessamento assiale e una maggior frequenza di avvio durante il secondo trimestre di farmaci bDMARDs.
Non è stata osservata una relazione tra il *timing* di sospensione della terapia con farmaci biotecnologici e lo sviluppo di *flare*, per quanto nel gruppo *flare* il farmaco biologico era stato più frequentemente stato sospeso al test di gravidanza positivo o nel primo trimestre (19% vs 6%, *p* n.s.).

Dalla analisi di questa casistica è stata redatta una tesi di laurea in Medicina e Chirurgia dal titolo 'Spondiloartriti sieronegative e gravidanza: analisi dell'attività di malattia ed esito gestazionale in 106 pazienti seguite prospetticamente' e un

abstract che ho presentato come '*poster tour*' al congresso EULAR 2022, tenutosi a Copenaghen a giugno 2022 (Allegato 13, tratto dalla Rivista *'Annals of the Rheumatic Diseases', EULAR European Congress of Rheumatology 2022, Abstracts*).

L'obiettivo futuro è di proseguire con la raccolta dei dati ai fini aumentare la numerosità delle gravidanze; questo consentirebbe infatti una migliore stratificazione della coorte sulla base della diagnosi e una migliore definizione dei potenziali fattori rischio di *flare.*

5. Capitolo 4: Il benessere psicologico nelle pazienti con malattia reumatologica durante la gravidanza e il post-partum

5.1 Introduzione e obiettivi

Il periodo perinatale è un periodo caratterizzato da cambiamenti che coinvolgono sia la sfera fisica che la sfera affettivo-relazionale ed è quindi una fase di grande complessità dal punto di vista psicologico.
Nella popolazione generale è noto come il periodo perinatale sia un periodo a rischio per lo sviluppo di depressione e ansia. In Italia, la prevalenza di tali disturbi è stimata tra il 10-15% delle donne nel post-partum mentre a livello globale è stimata intorno al 17%. (98, 99)
Diversi sono i fattori di rischio che possono intervenire nello sviluppo di depressione post-partum. Tra questi, ad esempio, è noto l'impatto di fattori socio-economici e demografici (scarso supporto sociale, basso reddito, prima gravidanza, giovane età possono essere fattori di rischio) così come il pregresso riscontro di depressione o ansia. È inoltre importante considerare variabili mediche e ostetriche legate al decorso della gravidanza stessa. (98, 100) La diagnosi di malattia reumatologica e il suo impatto sul decorso della gravidanza potrebbero costituire un fattore di rischio per lo sviluppo di questa condizione.
Ad oggi i dati riguardanti la frequenza della depressione post-partum nelle pazienti con malattie reumatologiche sono molto scarsi e limitati solo ad alcune patologie. (101) Recentemente, uno studio di popolazione ha mostrato come la frequenza di depressione post-partum fosse maggiore nei pazienti con diagnosi di AR, axSpA e PsA (17,2%) rispetto alla popolazione generale (12,8%), con un hazard ratio di 1,22 (95% CI 1,09-1,36). (102)

Tra gli strumenti di screening per valutare il rischio di depressione post-partum, uno dei più utilizzati è *l'Edinburgh Postnatal Depression Scale* (EPDS), un questionario di autovalutazione costituito da 10 domande che hanno lo scopo di indagare la presenza di sintomi ansioso-depressivi. (103) Lo screening è considerato a rischio per depressione post-partum in caso di punteggio $\geq$ 9 o in

caso di risposta positiva alla domanda 10, che indaga la presenza di pensieri suicidi. Una recente revisione sistematica della letteratura con meta-analisi in cui sono stati inclusi studi italiani in cui era stato utilizzato l'EPDS come strumento di screening per la depressione post-partum nella popolazione generale, ha evidenziato una prevalenza del rischio di depressione post-partum valutato con EPDS (*cut-off* ≥ 9) del 27,5%. (100) Tuttavia, gli studi in letteratura differiscono per quanto riguarda il *cut-off* considerato a rischio e diversi sono le limitazioni correlate a questo strumento. (104) Altri strumenti di screening potrebbero quindi essere utili ai fini di identificare le donne a rischio di depressione post-partum.
Un altro aspetto interessante emerso dalla sopracitata meta-analisi è che circa il 20% delle donne incluse presentava punteggi EPDS a rischio anche prima del parto. (100)

Considerando il grande impatto che lo sviluppo della depressione post-partum ha sul benessere psicologico della mamma e sullo sviluppo emotivo del neonato, la possibilità di una diagnosi precoce e di un rapido accesso a servizi dedicati appaiono fondamentali.
Data la rilevanza del problema e la necessità di identificare precocemente situazioni a rischio così come di definire l'entità del fenomeno nelle pazienti con malattie reumatologiche, in collaborazione con il Dipartimento di Ostetricia e con il Servizio di Psicologia Clinica Ostetrica dell'ASST Spedali Civili di Brescia, è stato organizzato ed avviato un programma di screening volto ad approfondire gli aspetti psicologici durante la gravidanza e nel post-partum delle pazienti afferenti all'ambulatorio multidisciplinare per le malattie autoimmuni sistemiche in gravidanza dell'U.O. di Reumatologia e Immunologia Clinica dell'ASST Spedali Civili di Brescia.

5.2 Risultati: valutazione del rischio di depressione post-partum ed implementazione dello screening per il disagio psicologico perinatale nelle pazienti affette da malattie reumatologiche

Il questionario EPDS viene somministrato alle pazienti incluse nel registro nazionale P-Rheum.it 30-60 giorni, 6 mesi e 12 mesi dopo il parto, come da protocollo.
Da una analisi preliminare dei dati relativi alle pazienti arruolate nel registro e seguite nell'ambulatorio dedicato alla gravidanza della nostra Unità Operativa fino a giugno 2022 (n= 129), è emerso che circa il 22% delle neomamme presentava un EPDS a rischio entro i 12 mesi post-partum. Non sono emerse differenze nella frequenza di positività tra le pazienti che presentavano una diagnosi di Artrite Infiammatoria o di Connettivite Sistemica (24% e 20% rispettivamente). Andando a ricercare potenziali fattori di rischio predittivi di screening positivo nel post-partum, è stato osservato come le pazienti risultate positive allo screening EPDS, presentassero già durante la gravidanza sintomi ansioso-depressivi rilevati tramite il questionario EuroQol.

Sulla base di questo riscontro, è stato quindi implementato lo screening per la depressione perinatale offerto alle pazienti afferenti all'ambulatorio multidisciplinare dedicato alle gravidanze.
Tale screening si avvale dell'utilizzo dell'EPDS e di altri specifici questionari di autovalutazione (Gad2, Whooley Question, MGMQ), somministrati dalle psicologhe alle pazienti con malattia reumatologica. Questi test sono stati somministrati alle pazienti non solo nel post-partum ma anche durante la gravidanza, per consentire l'individuazione precoce delle alterazioni della sfera emotiva meritevoli di valutazione specialistica, qualora la paziente lo desiderasse. Lo screening è stato quindi offerto alle pazienti nei 3 trimestri di gravidanza e ad 1-3-6-12 mesi nel post partum. In caso di screening positivo, alle pazienti è stato offerto un colloquio psicologico.
Da marzo 2022 ad agosto 2023 sono state arruolate 62 pazienti, di cui 38 sono risultate positive allo screening in almeno uno dei *timepoint* (di queste, 5 pazienti inizialmente risultate negativa allo screening, sono poi risultate positive durante la gravidanza). Circa il 66% delle pazienti positive, si è mostrata positiva anche alla valutazione clinica; di queste, il 52% ha accettato di avviare un percorso

psicologica, l’8% ha deciso di far riferimento ai servizi sul territorio, mentre il 40% ha rifiutato di essere seguita.

Tale progetto è ancora in corso e, nel futuro, consentirà di approfondire gli aspetti legati alla salute emotiva delle pazienti con malattia reumatologica durante la gravidanza e il post-partum.
I risultati preliminari di questi due studi sono stati presentati a settembre 2023 al congresso *Rheumapreg* (International Conference on Reproduction, Pregnancy and Rheumatic Diseases), come poster.

6. Capitolo 5: Altri progetti e collaborazioni

Oltre ai lavori scientifici presentati nei capitoli precedenti, nel corso dei 3 anni di Dottorato, ho avuto modo di approfondire alcuni aspetti specifici relativi la salute riproduttiva nei pazienti con malattia reumatologica partecipando alla stesura di alcune *review*. Queste hanno riguardato la Sclerosi Sistemica, l'andamento del post-partum nelle donne con malattia reumatologica e la gestione della Sindrome da Anticorpi Antifosfolipidi durante la gravidanza (quest'ultima sottomessa alla rivista *Oxford Rheumatology* e attualmente in via di pubblicazione). (101, 105)
Inoltre ho avuto la possibilità di redigere un editoriale di commento su una revisione sistematica della letteratura concernente gli outcome ostetrici e di attività di malattia durante la gravidanza e nel post-partum in pazienti con Spondiloartrite (assiale o psoriasica). (97, 106)

Quest'anno inoltre ho seguito, in qualità di P.I. per il l'U.O. di Reumatologia e Immunologia Clinica degli Spedali Civili di Brescia, la preparazione della documentazione e la sottomissione al Comitato Etico di due studi proposti nell'ambito del Gruppo di Studio della Medicina di Genere della SIR dai Colleghi dell'Ospedale San Raffaele di Milano (Centro coordinatore). Tali studi riguarderanno: 1) la raccolta dati delle gravidanze in pazienti con malattie reumatologiche sottoposte a tecniche di Procreazione Medicalmente Assistita e 2) lo studio dei marcatori di angiogenesi placentari nelle pazienti con sindrome da anticorpi antifosfolipidi.

Oltre alla partecipazione ai Congressi nazionali ed internazionali, precedentemente citati, per la presentazione degli abstract accettati, ho avuto la possibilità di partecipare come *invited speaker* al Congresso EULAR tenutosi a Copenaghen a giugno 2022, presentando un caso clinico riguardante la sindrome catastrofica da anticorpi antifosfolipidi durante la gravidanza nella sessione '*Clinical Challenge in Antiphospholipid Syndrome'*. Nel settembre 2022 ho partecipato a *Rheumapreg webinar*, dove sono stati presentati gli sviluppi del lavoro dei *working group* creati durante il Congresso del 2021 e le nuove

evidenze nell'ambito della salute riproduttiva nei pazienti con malattie reumatologica. Nel settembre 2023 sono stata invitata a moderare una sessione di poster durante il congresso *Rheumapreg* (*Poster Session 11: Vasculitis, Behcet and Autoinflammatory Diseases in Pregnancy*).

Nel 2023, sono risultata vincitrice dello *SLEuro Training Bursary Programme*, un programma promosso dalla Società Europea del Lupus Eritematoso Sistemico che fornisce l'opportunità a giovani reumatologi di frequentare per 8 settimane una Lupus Clinic Europea. Nel periodo dal 12/08/2023 al 06/10/2023 ho quindi frequentato il *Leeds Institute of Rheumatic and Musculoskeletal Medicine*, presso il Chapel Allerton Hospital di Leeds (UK). In questi due mesi ho avuto la possibilità di approfondire le mie conoscenze e capacità relative alla diagnosi precoce e alla gestione delle pazienti affette da Lupus Eritematoso Sistemico, frequentando la clinica dedicata a questi pazienti e confrontandomi con esperti internazionali del settore, in particolare per quanto riguarda l'utilizzo dei farmaci biologici Rituximab, Belimumab e Anifrolumab.

Parallelamente alle attività di ricerca, ho avuto la possibilità di partecipare attivamente a gruppi di studio e gruppi di giovani reumatologi, a livello nazionale ed internazionale, attraverso i quali ho potuto confrontarmi e scambiare esperienze ed opinioni con colleghi e pazienti.
Nel 2021 e nel 2022 sono stata membro della commissione SIRyoung (gruppo giovani della Società Italiana di Reumatologia) e, da giugno 2022, sono membro della *sub-committee Visibility and Global Affairs* di EMEUNET (*Emerging EULAR Network*, gruppo europeo di giovani reumatologi). Attraverso queste *membership* ho avuto modo di partecipare all'organizzazione di *webinar*, di eventi come le due edizioni del Campus SIRyoung (nel 2021 e nel 2023, a cui ho partecipato nel ruolo di tutor del *workshop* 'Il management di Lupus Eritematoso Sistemico, Connettiviti e Vasculiti') e di attività congressuali rivolte a giovani reumatologi. Inoltre, dal 2022 faccio parte di ERN young, gruppo di lavoro di ERN ReCONNECT (*European Reference Network on Connective Tissue and Musculoskeletal Diseases*). Proprio grazie ad una *call* partita da ERN, da febbraio

2023 sto collaborando in qualità di giovane reumatologa con il gruppo di giovani pazienti affetti da LES dell'Associazione Europea del Lupus (*Lupus Europe Youth group*). Durante il primo incontro in presenza (*Lupus Europe Youth meeting*) e le successive riunioni *online*, si è creata l'occasione di discutere di alcune tematiche importanti e di alcuni bisogni insoddisfatti, tra cui figuravano gli aspetti relativi la salute riproduttiva. Attualmente la collaborazione sta proseguendo e, nel futuro, vorremmo creare una *survey* da sottoporre sia a giovani reumatologi che a giovani pazienti per indagare il gap tra la percezione del medico e del paziente relativamente ad alcune tematiche quali la terapia, la salute riproduttiva e la transizione dal servizio di reumatologia pediatrica al servizio di reumatologia dell'adulto.

7. Discussione

Nel complesso, gli studi e le attività condotte hanno contribuito ad approfondire e diffondere alcuni aspetti cruciali, talvolta poco indagati, della salute riproduttiva nei pazienti con malattia reumatologica.

Questo tema ha una grande rilevanza nella comunità scientifica reumatologica, nonché nella pratica clinica. A livello europeo, l'EULAR ha recentemente pubblicato delle raccomandazioni per definire un '*core-dataset*' per i registri dedicati alla gravidanza, in modo da poter stimolare e facilitare la collaborazione multinazionale in questo campo. (36) A livello nazionale, la Società Italiana di Reumatologia negli ultimi anni ha promosso dapprima la creazione e lo sviluppo di un Registro nazionale dedicato alla raccolta prospettica dei dati delle gravidanze nei pazienti con malattia reumatologica, il P-Rheum.it, e successivamente ha individuato la salute riproduttiva come tematica per la realizzazione di Linee Guida per la pratica clinica in reumatologia. (36)
Entrambi i progetti, a cui ho potuto partecipare, hanno dato (e daranno) un contributo essenziale in questo ambito.
Il registro P-Rheum.it ha agevolato la raccolta prospettica dei dati relativi alle gravidanze in pazienti con malattie reumatologiche seguite in centri reumatologici italiani, consentendo, grazie alla collaborazione multicentrica, il raggiungimento di un numero elevato di arruolamenti. Questo risultato assume particolare rilevanza considerando che molte malattie reumatologiche sono malattie rare, per cui vi sono pochi dati in letteratura.
Una analisi preliminare nel 2022 condotta su 553 gravidanze per cui era disponibile l'outcome gestazionale aveva mostrato che la percentuale dei nati vivi era dell'89,5%. Tra i fattori che possono aver contribuito al raggiungimento di questa alta percentuale di outcome positivi, sono stati individuati il buon controllo di malattia nel preconcezionale e durante la gravidanza, ottenuti grazie anche all'utilizzo dei farmaci anti-reumatici. Attualmente l'arruolamento si è concluso ed è in corso l'estrazione dei dati delle gravidanze per cui è disponibile l'outcome gestazionale, cui seguirà un'analisi descrittiva dell'intera coorte. In futuro sarà

quindi possibile attingere ai dati del registro per andare ad approfondire aspetti specifici, nelle diverse patologie reumatologiche.
La pubblicazione delle prime linee guida italiane sulla salute riproduttiva nelle pazienti con malattia reumatologica rappresenta un significativo passo avanti importante in questo ambito, e fornisce ai clinici una guida condivisa per la gestione di alcune situazioni che si possono riscontrare nella pratica clinica. Fino a poco tempo fa, infatti, non esisteva in Italia un documento unico che andasse a trattare nello specifico l'argomento della salute riproduttiva nei pazienti con malattia reumatologica e il riferimento era dato dalle raccomandazioni e linee guida europee o americane.

Ai fini di migliorare l'outcome materno-fetale delle gravidanze in pazienti con malattia reumatologica, il counselling preconcezionale, la pianificazione e la gestione multidisciplinare della gravidanza sono elementi cruciali. Per poter meglio stratificare il rischio delle singole pazienti e definire un corretto timing per la ricerca della gravidanza, si devono valutare sia fattori di rischio generali che malattia-correlati. Tra questi ultimi, l'attività di malattia prima del concepimento e la terapia sono fattori particolarmente importanti.

Nel LES è noto come determinati fattori costituiscano un rischio per riacutizzazione di malattia in gravidanza o per l'insorgenza di complicanze ostetriche. Tra questi, una malattia attiva nei 6-12 mesi precedenti il concepimento è riconosciuto come fattore di rischio per lo sviluppo di *flare* durante la gravidanza e il raggiungimento della remissione o la bassa attività di malattia stabile in questo periodo sono quindi auspicabili. Tuttavia non è chiaro quale sia il livello di attività di malattia *target* da ottenere prima della gravidanza per favorire il miglior outcome materno-fetale.
In una casistica multicentrica di 304 gravidanze in pazienti affette da LES, sia la bassa attività di malattia che la remissione al preconcezionale sono stati riscontrati più frequentemente nelle gravidanze senza *flare* e in quelle senza complicanze ostetriche. (107) Tuttavia, in analisi multivariata, solo la remissione si è mostrata associata ad un miglior outcome. Ovviamente ulteriori studi,

prospettici, sono necessari per confermare questo dato. Questi risultati suggeriscono che le pazienti con bassa attività di malattia possono essere a rischio di sviluppare *flare* durante la gravidanza e che, nella pratica clinica, potrebbero essere meritevoli di *follow-up* più ravvicinati durante la gravidanza. Inoltre, dall'analisi multivariata abbiamo potuto confermare come l'interessamento renale anamnestico fosse un fattore di rischio indipendente per *flare*, mentre la terapia con idrossiclorochina fosse un fattore protettivo, sia per lo sviluppo di *flare* che per lo sviluppo di complicanze ostetriche. Questo dato è concorde con i risultati di precedenti studi e conferma l'importanza della valutazione di questi aspetti durante il counselling preconcezionale. (55, 108-111)

La conoscenza di questi fattori di rischio per complicanze nelle gravidanze in pazienti con LES è stata uno dei fattori che sicuramente ha contributo al miglioramento dell'outcome materno-fetale in queste pazienti. Tuttavia, vi è la necessità di definire ulteriori variabili e biomarcatori che si possano valutare nella pratica clinica prima del concepimento e che siano predittivi di complicanze.
Dato il possibile ruolo nella genesi dei *flare* di malattia e delle complicanze ostetriche nei pazienti con LES e APS, ai fini di indagare l'utilizzo del complemento come marker predittivo di complicanze, sono state analizzate due ampie casistiche in pazienti con LES e con APS.
Dall'analisi di 246 gravidanze in pazienti con diagnosi LES, è emerso che nelle gravidanze senza *flare* e senza complicanze ostetriche la variazione (ed in particolare l'incremento) dei livelli di C3 e di C4 durante la gravidanza presentava lo stesso andamento delle variazioni nelle gravidanze della popolazione ostetrica generale. (76) Tuttavia, i livelli sierici erano inferiori nelle gravidanze dei pazienti con LES rispetto a quelli della popolazione ostetrica generale. Inoltre, questa variazione fisiologica non è stata osservata nei gruppi di gravidanze con *flare* o con complicanze ostetriche. (76)
Degno di nota il fatto che il consumo del C4 al preconcezionale si sia mostrato fattore di rischio indipendente per *flare*. Questo potrebbe riflettere un ruolo preponderante dell'attivazione della via classica del complemento (mediata, ad esempio, dalla formazione degli immunocomplessi) nella genesi dei *flare* durante

la gravidanza nelle pazienti con LES. Inoltre, considerando che lo SLEDAI al preconcezionale non è risultato essere associato allo sviluppo di *flare* durante la gravidanza, questo potrebbe riflettere anche una condizione di attività di malattia subclinica che potrebbe portare alla riacutizzazione della malattia in presenza delle variazioni indotte dalla gravidanza. (76)

Per quanto riguarda le complicanze ostetriche, queste si sono verificate nel 19% dei casi. Stratificando la coorte in base al tipo di complicanza verificatasi, è emerso che le gravidanze esitate in perdita fetale o in parto pretermine severo non presentavano un incremento del C3 e del C4 durante il primo trimestre.

Per quanto la natura dei due studi e i pazienti inclusi siano diversi, questi risultati confermano quanto riportato dallo studio PROMISSE (*Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus*). (33) In questo studio prospettico, i livelli di C3 e/o C4 al basale così come l'incremento del C3 durante la gravidanza erano inferiori nelle gravidanze con eventi ostetrici avversi rispetto alle gravidanze senza complicanze. (33)

Nell'ambito di questa tesi, la metanalisi condotta su 4 lavori prospettici, che ha incluso un totale di oltre 500 gravidanze in pazienti con LES, ha evidenziato ulteriormente l'importanza del complemento prima e durante la gravidanza, non solo considerandone i livelli sierologici ma anche e soprattutto valutandone l'incremento durante il periodo gestazionale. (112) Infatti, il gruppo di gravidanze in cui si è verificato un *flare*, ha presentato un incremento minore di C3 e di C4 tra il concepimento e il primo trimestre. (112) Inoltre, il mancato incremento del C3 tra il primo trimestre si è mostrato associato ad un aumentato rischio di complicanze ostetriche. (112)

L'analisi condotta su 260 gravidanze in pazienti con APS o aPL positivi ha confermato il possibile ruolo del complemento come marker predittivo di complicanze ostetriche anche in questa categoria di pazienti. (113) Infatti, nel gruppo di gravidanze esitate con evento avverso sono stati riscontrati livelli di complemento inferiori rispetto alle gravidanze decorse senza complicanze. Degno di nota il fatto che le pazienti con triplice positività per aPL presentavano

una riduzione del complemento nel 77% circa dei casi e che questa fosse associata allo sviluppo di complicanze quali gli aborti. (113) Inoltre, un altro risultato importante emerso da questo lavoro è che l'aggiunta della terapia con idrossiclorochina alla terapia di combinazione (basse dosi di acido acetilsalicilico ed eparina) nel gruppo pazienti con triplice positività e con riduzione del complemento, era legata ad una riduzione del rischio di sviluppare complicanze. (113)
Questi risultati sono stati recentemente confermati in 1048 gravidanze in pazienti con APS ostetrica dall'*European Registry of OAPS*. (114) Le gravidanze in pazienti che presentavano livelli bassi di complemento al preconcezionale, presentavano più frequentemente una restrizione tardiva della crescita fetale, avevano una durata della gestazione inferiore e una percentuale di nati vivi inferiore rispetto al gruppo con normali livelli preconcezionali di complemento. (114)

In generale, questi risultati confermano l'utilità del monitoraggio delle frazioni C3 e C4 del complemento durante la gravidanza e ne supportano il loro utilizzo come strumento aggiuntivo da considerare per la stratificazione del rischio individuale durante il counselling preconcezionale.

Un ulteriore aspetto da valutare durante il counselling preconcezionale è la terapia. Le modifiche terapeutiche devono avere l'obiettivo di consentire il mantenimento di un buon controllo della attività di malattia anche durante la gravidanza e devono ovviamente comprendere farmaci compatibili, che non siano dannosi per il feto. Tuttavia l'indicazione alla sospensione di alcuni farmaci al test positivo è spesso dettata dalla mancanza di dati in letteratura, più che da una comprovata incompatibilità. Questo è quello che succede ad esempio nelle raccomandazioni relative all'utilizzo di belimumab durante la gravidanza.
Nell'esperienza derivata dalla casistica italiana in cui sono state incluse 24 gravidanze in pazienti con LES trattate con belimumab, è stato registrato un solo caso di *flare* cutaneo dal primo trimestre nel gruppo di pazienti che avevano proseguito la terapia mentre sono stati registrati 3 *flare*, tutti nel terzo trimestre,

nel gruppo di pazienti in cui la terapia era stata sospesa al test di gravidanza positivo. La terapia dei *flare* ha richiesto l'utilizzo steroide *per os* e, in due casi, è stata necessaria la somministrazione endovena. Nei neonati di questa casistica, non sono state registrate malformazioni attribuite all'utilizzo della terapia e non sono state riportate infezioni alla nascita; in un caso si è verificata una sepsi a partenza da una probabile infezione delle vie urinarie a due mesi dalla nascita.
Per quanto limitati e non definitivi, i dati presenti in letteratura non hanno mostrato effetti avversi chiaramente correlati all'utilizzo di belimumab. (115-118) Gli sforzi futuri dovranno essere rivolti alla migliore definizione del profilo delle pazienti che potrebbero avere un rischio maggiore di riacutizzazione di malattia durante la gravidanza in caso di sospensione della terapia al test positivo. Questo consentirebbe una migliore stratificazione del rischio individuale e fornirebbe maggiori elementi per la valutazione del rischio-beneficio nella decisione del *timing* di sospensione del farmaco.

Sempre nell'ambito del counselling preconcezionale relativo alle modifiche terapeutiche, si deve considerare, nelle pazienti affette da LES, la possibilità di inserire delle terapie aggiuntive, che possono avere un impatto favorevole sull'outcome sia materno che fetale.
Attualmente non sono presenti evidenze che supportino in maniera sistematica l'utilizzo di acido acetilsalicilico a basso dosaggio in tutte le pazienti con LES. Tuttavia, considerando l'aumentato rischio di complicanze quali la pre-eclampsia, ne è raccomandato l'avvio, soprattutto in presenza di pregresso interessamento renale o di positività per aPL. (119) Per meglio definire il possibile impatto di questa terapia sull'outcome ostetrico, sono stati valutate 216 gravidanze in pazienti con LES che non presentassero coinvolgimento renale né positività degli aPL. Per quanto, in questo selezionato gruppo di pazienti, non vi fossero differenze significative nella frequenza di outcome avversi tra chi assumeva o no la terapia con acido acetilsalicilico a basso dosaggio, è stata comunque osservata una percentuale maggiore di pre-eclampsia nelle pazienti non trattate. Dato il limitato numero di pre-eclampsie (6,1%) registrate nella coorte, ulteriori studi appaiono necessari per meglio definire il ruolo di questa terapia in pazienti

selezionate, senza interessamento renale e senza aPL. Inoltre, per quanto fattori di rischio quali l'ipertensione, l'obesità e l'abitudine tabagica siano stati presi in considerazione nel presente studio, diversi sono i fattori che devono essere presi in considerazione e la gestione multidisciplinare in questo ambito è fondamentale.

Nelle artriti infiammatorie i fattori di rischio per *flare* di malattia durante la gravidanza non sono stati del tutto indagati. Questo può essere legato da un lato all'evidenza, in passato, di un miglioramento dell'attività di malattia e dall'altro a ragioni epidemiologiche. In realtà oggi si ha sempre più consapevolezza del fatto che anche le pazienti con artrite possono avere una riacutizzazione di malattia durante la gravidanza e nel post-partum. Il *timing* di sospensione della terapia con farmaci biotecnologici, ed eventuali loro modifiche, deve quindi essere attentamente valutato durante il counselling preconcezionale.
In una coorte monocentrica di 73 gravidanze in pazienti con AR, abbiamo registrato una frequenza di *flare* del 37% durante la gravidanza e del 40% nel post partum. Lo sviluppo di *flare* si è mostrato associato alla sospensione del farmaco biologico al test di gravidanza positivo. Questo dato conferma ciò che è stato descritto anche in altre casistiche in letteratura. (32, 79) Inoltre, è stata osservata una maggiore frequenza di *flare* nel gruppo di pazienti che prima della gravidanza avevano ricevuto più linee di farmaco biologico; questo potrebbe delineare un gruppo di pazienti con malattia più aggressiva (o difficile da trattare). Quindi questi risultati indicano che pazienti con malattia attiva e con un fenotipo di malattia più aggressivo (che ha richiesto l'utilizzo prima della gravidanza, di diversi farmaci biotecnologici), potrebbero essere a maggior rischio di *flare* durante la gravidanza e che, in questo particolare gruppo di pazienti, il *timing* di sospensione dell'anti-TNFα debba essere attentamente valutato in quanto potrebbe costituire un ulteriore fattore di rischio per lo sviluppo di *flare.* Questo ha un impatto non solo sulla qualità di vita della paziente, ma riveste un ruolo importante anche per l'outcome gestazionale. In questa coorte, infatti, è stata riscontrata una maggiore attività di malattia nel primo trimestre nelle gravidanze esitate in parto pretermine. In altre casistiche, ma non nella presente, sia l'attività

di malattia che l'utilizzo di corticosteroidi si erano associati a questa complicanza. (82)

Nell'ambito di questa tesi, la frequenza dei *flare* è stata riscontrata nel 40% anche nella coorte bi-centrica di pazienti con SpA, sia durante la gravidanza (dove si sono verificati spesso nel secondo trimestre) che nel post-partum. Inoltre, l'interessamento assiale, indipendentemente dalla diagnosi di SpA o PsA, si è mostrato un potenziale fattore di rischio per *flare*.
Ursin *et al.*, valutando una coorte di 179 gravidanze in pazienti con axSpA, hanno osservato una maggiore attività di malattia (valutata mediante BASDAI) durante il secondo trimestre di gravidanza, quando il 45% delle pazienti presentava malattia attiva. (92) Inoltre, un peggioramento della funzionalità fisica (valutata mediante BASFI) è stato osservato nel secondo e terzo trimestre. (92) Nelle pazienti con PsA, invece, l'attività di malattia si era mostrata stabile durante la gravidanza per peggiorare nei 6 mesi dopo il parto. (120) Come evidenziato da una recente revisione sistematica della letteratura, questo si può verificare fino al 100% dei casi. (97)
Nel nostro studio, non sono emerse associazioni tra lo sviluppo di *flare* e il timing di sospensione della terapia biologica, anche se nel gruppo di gravidanze che avevano sviluppato *flare* vi era una tendenza alla più frequente sospensione della terapia al test positivo (non significativo). Altri studi hanno invece mostrato come la sospensione dell'anti TNFα fosse associata all'attività di malattia in gravidanza. (32, 92, 120)
Anche in questo contesto, quindi, le modifiche terapeutiche e il *timing* di sospensione della terapia con farmaci biologici devono essere attentamente valutati al momento del counselling preconcezionale. Ulteriori studi appaiono necessari per poter meglio definire il profilo di paziente a maggior rischio di *flare* durante la gravidanza.

Infine, un altro aspetto approfondito nell'ambito di questa tesi, è stato quello del benessere emotivo delle pazienti durante la gravidanza e nel post-partum.

Da una prima analisi della nostra casistica locale, è emerso che il 24% delle donne con Artrite Infiammatoria e il 20% delle donne con Connettivite, presentava un EPDS nel post-partum a rischio per depressione post-partum. Degno di nota il fatto che queste pazienti presentassero già durante la gravidanza aspetti di ansia, rilevati mediante il questionario EuroQoL. È stato quindi avviato uno screening più esteso, anche durante la gravidanza, in collaborazione con il Servizio di Psicologia. Da una preliminare analisi è emerso che circa 6 pazienti su 10 presentavano uno screening a rischio in almeno uno dei momenti considerati. I dati in letteratura sono molto scarsi ma evidenziano come la depressione post-partum possa essere più frequente nelle donne con malattie reumatologiche rispetto alla popolazione generale. (101, 102)
Data la rilevanza del problema, lo screening per la depressione post-partum dovrebbe essere esteso a tutte le donne con malattia reumatologica. Semplici strumenti, come l'EPDS, possono aiutare il clinico ad individuare una paziente a rischio. Anche in questo ambito, la valutazione e la gestione multidisciplinare, con il supporto di psicologhe cliniche, è fondamentale.

In conclusione, le attività svolte nel contesto del presente progetto di Dottorato hanno contribuito a chiari numerosi aspetti relativi alla salute riproduttiva nelle donne con malattie reumatologiche, fornendo dati preziosi sull'outcome-materno fetale e sull'utilizzo delle terapie e contribuendo a meglio definire alcuni fattori di rischio e biomarcatori predittivi di eventi avversi. Complessivamente, le informazioni raccolte hanno confermato l'importanza della gestione multidisciplinare e del monitoraggio attento della gravidanza e del post-partum nella pratica clinica quotidiana per queste pazienti.

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Francesca Crisafulli

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9. Allegati

Allegato 1

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Reumatismo

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RESULTS FROM THE PROSPECTIVE NATIONWIDE P-RHEUM.IT STUDY (THE ITALIAN REGISTRY OF PREGNANCY IN THE RHEUMATIC DISEASES) PROMOTED BY THE ITALIAN SOCIETY FOR RHEUMATOLOGY

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Objectives. The P-RHEUM.it study was established to study the course and outcomes of pregnancies in women with rheumatologic diseases (RDs) as well as to increase knowledge about the use and safety of treatments during pregnancy and lactation.

The aim of this study was to describe the maternal-fetal and neonatal outcomes of prospectively-followed pregnancies from the P-RHEUM.it study.

Materials and Methods. The Italian P-RHEUM.it study is designed as a nationwide, web-based longitudinal observational cohort study to collect data on pregnancies in rheumatologic diseases. The course of maternal disease, medications, development of fetus and complications are reported for each trimester. After delivery, maternal health, pregnancy outcome and child development are collected.

Results. From May 2018 to April 2021, 536 pregnancies in 532 patients (median gestational week at enrolment: 11 [IQR 8-15]) were enrolled in 28 Centers (Table I). 44% (199/452) of women received pre-conception counselling and the median time to pregnancy was 3 (0-6) months. In 5.4% of cases, pregnancies were obtained through assisted reproductive technologies.

At enrolment, a good disease control was observed, as evaluated by physician global assessment [IQR] 4/100 [0-19], patient global health [IQR] 80/100 [70-92] and EuroQol [IQR] 1 [0.8-1]. Flare occurred in 32 (6%) pregnancies.

Among 240 pregnancies with complete data on pregnancy course, hypertensive disorders of preg-

Age, median (IQR), years	34 (31-37)
Disease duration, median (IQR)	6 (2-11)
Ethnicity	
Caucasian	87%
Afro-american	2%
Asian	3%
Latin-american	3%
Arabic	4%
Other	1%
Education level	
Primary school	8%
Secondary school	28%
University/master	32%
Unknown	32%
Smoking habit	
Occasionally	7%
Regularly	1%
Past	20%
Rheumatoid arthritis	13%
Spondyloarthritis	15%
Juvenile Idiopathic Arthritis	5%
Systemic Lupus Erythematosus	18%
Undifferentiated Connective Tissue Disease	17%
Other Connective Tissue Diseases	12%
Primary Antiphospholipid Syndrome/ Antiphospholipid antibodies carrier	14%
Systemic Vasculitis	4%
Other	2%
Associated autoimmune diseases	24%
Autoimmune thyroiditis	13%

nancy were registered in 10 cases (8 hypertension, 2 pre-eclampsia), of which 6 occurred in SLE patients; 8 Intra-Uterine Growth Restriction were recorded.

Complete data on pregnancy outcome were available for 302 pregnancies. Live births were 265 (88%; median gestational age at delivery 39, IQR 37-40); 28 miscarriages, 6 fetal death and 3 elective abortions occurred. Two perinatal deaths were recorded. Preterm births were 34/265 (13%) of which 11 occurred before the 34th week. Newborns were male in 49% of cases; 4% was Small for Gestational Age; in 6 cases malformations were recorded.

254 and 101 patients completed the one- and 6-month follow-up; 77% and 49% respectively was breastfeeding. Two months after delivery, 17% of patients had an EPDS (Edinburgh Postnatal Depression Scale) at risk for post-partum depression and 6 months after delivery 13/95 (14%). 135 children had a complete 6-months follow-up: 39 received mandatory vaccinations (1 case of complications was recorded).

Conclusions. Data from the P-RHEUM.it study highlight that the course and the outcomes of prospectively-followed pregnancies in women with RDs is overall good. Hypertensive disorders and IUGR were among the most reported complications albeit in a small number of pregnancies.

A high percentage of breastfeeding after delivery and after 6 months was observed and the frequency of post-partum depressive symptoms seems to be similar of that of the general population.

Keywords: *Pregnancy, P-RHEUM.IT, Registry.*

Allegato 2

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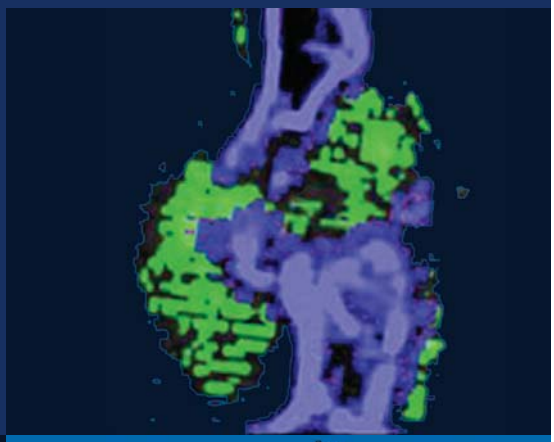

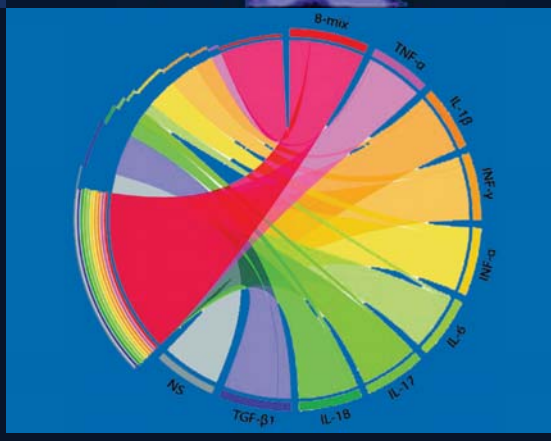

Abstracts

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OP0125 THE MANAGEMENT OF PREGNANCY IN AUTOIMMUNE RHEUMATIC DISEASES: ANALYSIS OF 758 PREGNANCIES FROM THE PROSPECTIVE NATIONWIDE P-RHEUM.IT STUDY (THE ITALIAN REGISTRY OF PREGNANCY IN THE RHEUMATIC DISEASES)

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Background: Pregnancy is a topic of fundamental importance for women living with autoimmune rheumatic diseases (ARD). Efforts at national and international levels have been put in the collection and harmonization of data in order to implement an evidence-based management of pregnant patients.

Objectives: The P-RHEUM.it study was designed as a nationwide, web-based longitudinal observational cohort study to collect data about pregnancy in ARD in 26 centers in Italy. The study started in May 2018 and has been supported by the Italian Society for Rheumatology.

Methods: Pregnant patients with a definite rheumatic disease according international criteria were enrolled up to gestational week (GW) 20. The course of maternal disease activity, the use of medications, fetal and maternal complications, and the quality of life (EuroQoL questionnaire) were collected for each trimester, as well as pregnancy outcome, mode of delivery, neonatal complications, and maternal and children's follow-up to 6 months after delivery, including the screening for post-partum depression by means of EPDS (Edinburgh Postnatal Depression Scale).

Results: As of December 2021, 758 pregnancies had been enrolled, 205 (27%) ongoing and 553 (73%) with outcome. Pregnancy loss occurred in 54 (9.8%) cases (40 spontaneous miscarriages; 6 voluntary terminations). Live births were 495 (89.5%), perinatal death occurred in 4 (0.7%) cases. Table 1 reports on the group of 495 live births, along with subgroups of Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE), the two most represented diseases. Regarding treatments, 166 (30%) pregnancies were exposed to corticosteroids, 239 (43%) to hydroxychloroquine, 59 (10.7%) to csDMARDs, 84 (15.2%) to TNF inhibitors, 1 (0.2%) to non-TNFi bDMARDs, 299 (54%) to low dose acetylsalicylic acid, and 126 (22.8%) to heparin.

Table 1.

PREGNANCIES WITH LIVE BIRTHS, EXCLUDING PERINATAL DEATHS	Total pregnancies (n=495)	RA pregnancies (n=69)	SLE pregnancies (n=93)
Age at conception (years)	34 (31 - 37)	34.5 (32 - 38)	34 (31 - 36)
Disease duration (years)	6.1 (2.2 - 11.1)	7.1 (4.3 - 11.6)	9.3 (5.9 - 15.9)
Caucasian	431 (87.8%)	53 (79.1%)	75 (80.6%)
Never smokers	358 (73.8%)	53 (80.3%)	66 (71.7%)
Body Mass Index >30	45 (9.5%)	7 (10.3%)	5 (5.6%)
Arterial Hypertension	6 (1.2%)	0 (0%)	2 (2.2%)
Time to pregnancy (months)	3 (1 - 6)	3 (1 - 6)	3 (0 - 10)
Physician-reported flares in the 12 months prior to conception	107 (23%)	22 (34.4%)	13 (14.8%)
Physician global assessment at enrolment (VAS 0-100)	5 (0 - 17)	5 (0 - 20)	4 (0 - 10)
Patient global health at enrolment (VAS 0-100)	18 (7 - 30)	10 (5 - 29)	10 (5 - 25)
EuroQoL at enrolment (-1.6 – 1)	1 (0.8 - 1)	1 (0.8 - 1)	1 (0.8 - 1)
Flares during pregnancy	35 (7.1%)	6 (8.7%)	7 (7.5%)
Hypertensive disturbances*	8 (1.7%)	1 (1.6%)	6 (6.6%)
Delivery at term (≥37 GW)	410 (85.1%)	53 (77.9%)	74 (80.4%)
Spontaneous vaginal delivery	173 (35.9%)	23 (33.8%)	23 (25.3%)
Congenital malformations	11 (2.4%)	2 (3.1%)	1 (1.1%)
Small for gestational age (SGA) neonate	24 (4.9%)	1 (1.4%)	9 (9.9%)
Breastfeeding in the first 4 weeks after delivery	341 (79.7%)	45 (77.6%)	59 (76.6%)
EPDS score at risk for post-partum depression	22 (14.1%)	0 (0%)	3 (10.3%)

Continuous variables are expressed as median (interquartile range); *gestational hypertension/preeclampsia/HELLP syndrome/eclampsia.

Conclusion: Multiple factors may have contributed to the high rate of live births, including good disease control before and during pregnancy thanks to the use of anti-rheumatic drugs and low frequency of general risk factors. SLE pregnancy was affected by a higher frequency of complications (hypertensive disturbances, SGA babies) as compared to RA pregnancy. Nearly 80% of patients breastfed in the first month after delivery. For the first time, data about the screening questionnaire for post-partum depression were collected, showing at least 1 out 10 patients can be at risk.

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OP0126 ARE WOMEN WITH SPONDYLOARTHRITIS AT INCREASED RISK OF ADVERSE MATERNAL AND INFANT OUTCOMES? – A SWEDISH COHORT STUDY

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Background: An increased risk of adverse pregnancy and neonatal outcomes has been reported for pregnancies in women with several rheumatic diseases including rheumatoid arthritis and psoriatic arthritis. In spondyloarthritis (SpA), findings have not been uniform, with some studies reporting increased risks of Cesarean delivery, preterm birth, infants born small-for-gestational-age (SGA), and gestational diabetes- and hypertension, while others have failed to identify any significant differences between women with SpA and general population control women. Most studies reporting no differences have either been small or lacked an appropriate comparison group [1].

Objectives: To assess the risk of adverse maternal and infant pregnancy outcomes in women with SpA compared to the general population.

Methods: In this nationwide register-based study, we included singleton births between April 2007 and December 2019 in women diagnosed with ankylosing spondylitis (AS; ICD-10 codes M45 or M08.1) or undifferentiated SpA (uSpA; ICD-10 codes M46.8 or M46.9). This was performed through linkage between the National Patient Register and the Medical Birth Register. Each birth was matched on birth year, maternal age, and parity to ten comparator births in women free from chronic inflammatory arthritis at time of birth. Relative risks (RR) of adverse outcomes were estimated by Poisson regression, adjusting for

Allegato 3

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The Journal of Rheumatology

Variations of C3 and C4 Before and During Pregnancy in Systemic Lupus Erythematosus: Association With Disease Flares and Obstetric Outcomes

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ABSTRACT. ***Objective.*** To analyze complement level variations in systemic lupus erythematosus (SLE) pregnancies, focusing on disease flares and obstetric complications.

Methods. SLE pregnancies prospectively followed by multidisciplinary teams from 1987 to 2018 in 2 Italian rheumatology centers were retrospectively analyzed. As reference, pregnancy-modified ranges of normal levels of C3 and C4 were derived from 175 pregnancies from the general obstetric population (GOP), as previously described by our group.

Results. Two hundred forty-six pregnancies in 172 patients with SLE were analyzed. Eighty-nine percent were live births. Thirty-five flares were recorded in 30 pregnancies (12.2%) and obstetric complications occurred in 47 pregnancies (19.1%) including 27 pregnancy losses, 11 severely preterm births (2 resulting in perinatal death), and 15 hypertensive disorders. C3 and C4 levels were higher in the GOP than in patients with SLE, at any time point. C3 and C4 levels progressively increased during pregnancy in both GOP and SLE pregnancies without flare and obstetric complications, whereas this physiological increase was not observed in pregnancies with flares or obstetric complications. A significantly higher frequency of low C4 was found in pregnancies with flares (at preconception and in each trimester) and preterm births (at preconception). In multivariate analysis, low C4 at preconception was associated with flares (odds ratio 13.81, 95% CI 3.10-61.43, $P < 0.001$).

Conclusion. Low C4 at preconception was found to be an independent risk factor for SLE flare during pregnancy. Not only C3 and C4 levels but also their variations should be observed, as their failure to increase can be useful to predict risk of complications and suggest closer monitoring.

Key Indexing Terms: complement C3, complement C4, pregnancy, systemic lupus erythematosus

Allegato 4

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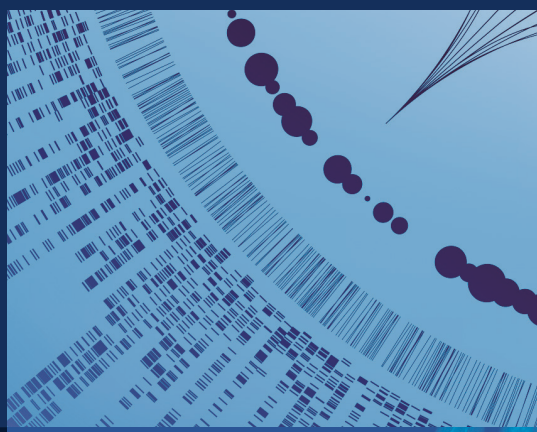

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Table 1. Initial symptoms prior to diagnosis

Symptoms	*N=438 (%)*	*Duration* (mean months ±SD)*
Arthralgias	326 (74.4)	37.5 ±69.4
Photosensitive rash	223 (50.9)	30.6 ±70.2
Malar rash	168 (38.3)	22.6 ±62
Alopecia	167 (38.1)	19.6 ±54.6
Ulcers	106 (24.2)	16.8 ±54.4
Fever	103 (23.5)	9.3 ±43.8
Raynaud's phenomenon	146 (33.3)	22.3 ±68.5
Fatigue	233 (53.1)	19.7 ±45.7

*Mean time from symptom onset to established diagnosis

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Disclosure of Interests: None declared
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POS0760

MONITORING C3 AND C4 VARIATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS PREGNANCIES IS USEFUL TO RECOGNIZE COMPLICATIONS. DATA FROM 2 ITALIAN CENTERS

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Background: In SLE pregnancies adverse pregnancy outcomes (APO) are more frequent than in general obstetric population (GOP). In clinical practice, low C3 and C4 levels are associated with active disease and, during pregnancy, complement activation products are shown to be associated with APO.
Objectives: To analyse complement variations during SLE pregnancies, focusing on disease flares and APO.
Methods: Data on SLE pregnancies prospectively-followed by multidisciplinary team in 2 Italian Centers from 1987 to 2018 were retrospectively analysed. C3 and C4 normal levels were calculated in general obstetric population (GOP) as previously described[1], and related to maternal and fetal outcome. Non categorical variables were compared using Mann-Whitney test or Wilcoxon test when appropriate.
Results: Two hundred forty-six pregnancies in 172 SLE patients were analysed (mean age at conception 31.3 ±4.9 years; mean disease duration 8.3 ±7.1). Anti-Ro antibodies were positive in 64 patients (37%) and anti-phospholipid antibodies (aPL) were positive in 84 (48%), with single positivity in 54%, double in 24% and triple in 21%; 9 patients (5%) had also a diagnosis of obstetric-antiphospholipid syndrome (APS) and 8 (4%) had thrombotic-APS. Seventy-one patients (41%) had history of Lupus Nephritis.
Thirty-five flares were recorded in 30 pregnancies (12%). APO occurred in 47 pregnancies (19%) and were: 27 fetal loss (20 early miscarriage <10th week and 7 intrauterine fetal death), 11 severe preterm birth (<34th week) and 15 hypertensive disorder (11 pre-eclampsia and 5 pre-eclampsia+HELLP syndrome).

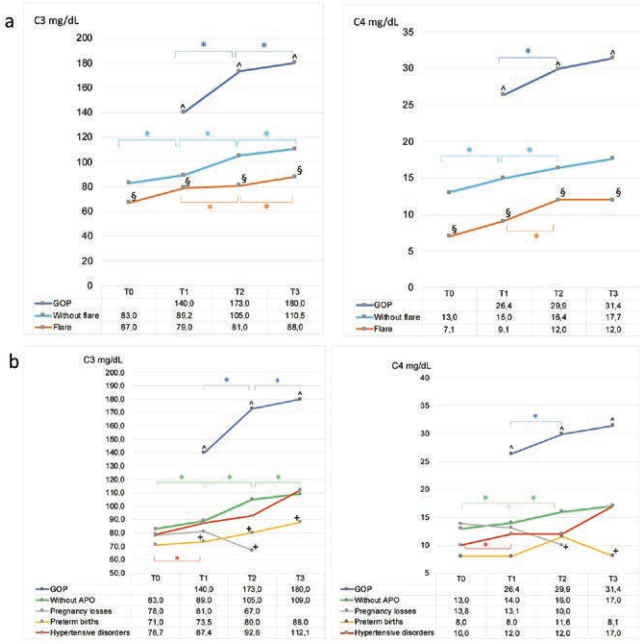

Figure 1. Variations of C3 and C4 median levels (mg/dL) throughout pregnancy in GOP[1] and in SLE pregnancies without and with flare (a) and without and with APO (b).

In GOP, C3 progressively increased throughout pregnancy and C4 increase from the 1st trimester to the 2nd trimester, as well as in SLE pregnancies without flares and without APO, from preconception (Fig 1). In the other SLE groups, C3 and C4 showed a different trend: in pregnancies with flares, they did not increase from preconception to the 1st trimester; in fetal losses and severe pre-term births, they remained stable throughout pregnancy; in hypertensive disorders they increased only between preconception and the 1st trimester.
C3 and C4 levels were higher in GOP than in all SLE pregnancies groups (including those without flares and without APO) in each trimester. SLE pregnancies without flares showed higher C3 and C4 levels than pregnancies with flares, at preconception and in each trimester. SLE pregnancies without APO had higher C3 and C4 levels than pregnancies with fetal death at 2nd trimester, higher C3 levels than severe pre-term births in each trimester and higher C4 at 3rd trimester (Fig.1).
At preconception, pregnancies with flares showed a higher frequency of low C3 and of low C4 than in pregnancies without flares (76% vs 42%, p=0.01; 76% vs 26%, p<0.001, respectively). Using the normality range previously calculated in GOP, SLE pregnancies with flares had higher frequency of low C4 in every trimester as compared with pregnancies without flares (1st: 82% vs 48%, p=0.003; 2nd: 82% vs 64%, p=0.01; 3rd: 64% vs 30%, p=0.002). At multivariate analysis, low C4 at preconception was associated with flare (OR [95% CI]: 10.34 [2.52-42.39]; p=0.001).
** p <0.05*
^as compared with SLE groups: p<0.05; § as compared with SLE pregnancies without flare: p<0.05; + as compared with SLE pregnancies without APO: p<0.05
Conclusion: In SLE pregnancies, monitoring of C3 and C4 is important: its failure to increase can be useful to recognize potential risk situations which deserve particular monitoring.

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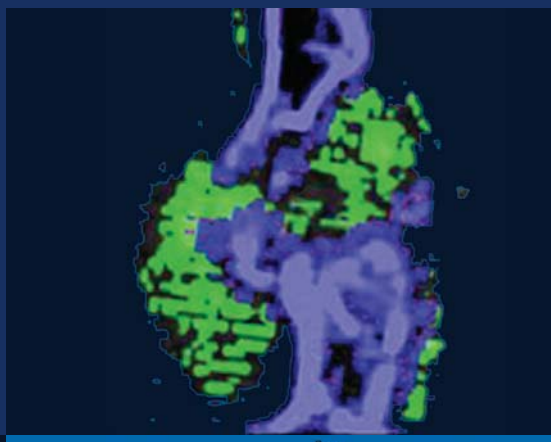

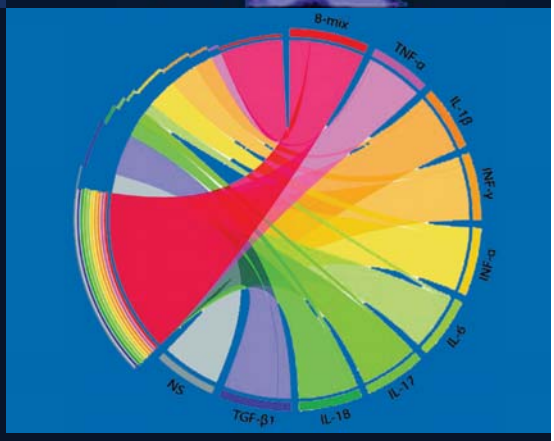

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Oral Presentations

Addressing the effect of Placebo, Nocebo and Contextual factors in RMDs

OP0001

"I WILL NEVER FORGET THE SHAME I FELT": A SURVEY TO PEOPLE WITH A RHEUMATIC DISEASE ABOUT INVALIDATION FROM HEALTH PROFESSIONALS AND OTHER PEOPLE

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Background: The term invalidation refers to the patients' perception that their medical condition is not recognised, either in denying, lecturing, not supporting or not acknowledging the condition. This may be the felt from health professionals themselves but also from family, friends, at work and in other social areas, imposing great suffering.[1] The European Alliance of Associations for Rheumatology (EULAR) has made efforts to raise awareness for the burden imposed by rheumatic and musculoskeletal conditions (RMDs) and promote the best quality of care, including recognition and psychosocial support. However, it is unclear how frequent and severe the problem remains nowadays.
Objectives: The aims of this national survey were: (i) to identify the levels of invalidation and lack of understanding felt by adults with RMDs from health professionals and other people, (ii) to investigate the relationship between invalidation, sociodemographic characteristics and disease; and (iii) to understand its impact on people's life and health outcomes.
Methods: An online survey was developed by the national health professionals in rheumatology and patients' organisations and opened between May and December of 2021. The questionnaire included demographic and disease information, the Illness Invalidation Inventory (3*I),[1] with additional questions in a Likert format and open questions for a detailed understanding of the phenomenon. The 3*I is composed of 8 items, measured from 1 (=never) to 5 (=very often), forming two factors: Discounting (mean of 5 items; lower scores indicating more discounting) and Lack of understanding (mean of 3 items; Higher scores representing higher lack of understanding).
Quantitative data were analysed using descriptive statistics. Associations were tested with a t-student and ANOVA one-way test (Bonferroni correction). Open responses were categorised using the content analysis technique, and themes were defined *a posteriori*.
Results: From the > 1500 responses obtained, 1410 responses were filled out completely (mean age of 46 years [SD=11], 95% females, 60% with FM, among which 59% were diagnosed in the last 5 years).
Invalidation was reported by 86% of the participants and 70% rated ≤5 on a scale from 0 (nothing) to 10 (totally) on feeling understood by other people. Invalidation was mostly felt from family (56%), health professionals (48%), friends (39%) and social environment (38%). The impact of this invalidation is mainly on the psychological well-being (58%), also reducing seeking health care (41%) and therapeutic adherence (17%), affecting work (41%), and to a less extent, (family) relations (31%).
Figure 1 shows the frequency of responses and means scores on the 3*I items and factors for participants with and without FM. The burden is greater for people with FM, which was statistically significant. People with higher education felt more discounting and more lack of understanding. No differences (p>0.05) were observed for gender or civil status.
Elucidative expressions of invalidation were shared, mostly by people with FM, encompassing their ability to work and need for social support, faking pain and treatment efficacy, and even intimacy aspects. These emotionally uncomfortable situations can be linked to lesser engagement with healthcare and disease management, and therefore, with worse health outcomes.
Conclusion: Invalidation remains a source of suffering, affecting well-being and health outcomes. Specific awareness and educational campaigns are needed to target this problem on different play-actors.

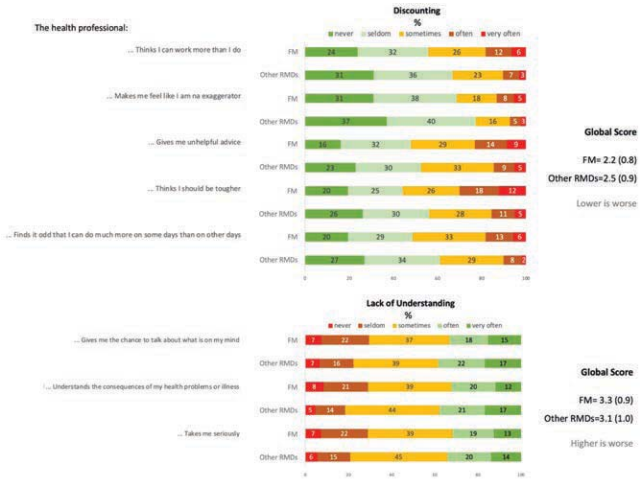

Figure 1. Percentages of responses per type of disease for the eight items of the Illness Invalidation Inventory.

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DOI: 10.1136/annrheumdis-2022-eular.4969

Bench to Bedside: The complement system in rheumatic diseases

OP0002

LOW COMPLEMENT LEVELS IN THE FIRST TRIMESTER PREDICT DISEASE FLARE IN SLE PREGNANCY: A NETWORK META-ANALYSIS ON 532 PATIENTS.

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Background: The complement system is a key-player in the pathogenesis of systemic lupus erythematosus (SLE); its decreases correlate with disease activity and precedes flare. Since synthesis of complement proteins increase during gestational course, it is debated whether complement levels exert a prognostic role in pregnant women with SLE.
Objectives: We performed a network meta-analysis to assess the prognostic role of complement in pregnant SLE women, to evaluate the possible role of complement fluctuations during pregnancies.
Methods: Data from available prospective studies (Jan 2002-Dec 2020) investigating pregnancies in at least 50 SLE patients, excluding miscarriages before 12 weeks, were pooled together. After a systematic literature search, corresponding authors of 19 retrieved studies meeting inclusion criteria were invited to contribute with additional data, including complement levels [6 months before pregnancy, at conception, 1st trimester (T1), 2nd trimester (T2), 3rd trimester (T3) and 3 months after delivery].
Results: A total of 532 SLE women from four eligible studies were included in the analysis [1-4]. Lupus Nephritis (LN) was diagnosed in 237 patients (44.5%) and Antiphospholipid Syndrome in 68 (12.8%). A total of 170 patients (32%) experienced a flare during pregnancy, defined as need of new Immunosuppressants or increase of prednisone > 9 mg/day.
Patients with LN had significantly lower mean levels of complement (C3 at conception; C3 at T1; C3 after 3 months of delivery; C4 at all timepoints except for C4 at T3). SLE patients who experienced flares during pregnancy had significantly lower mean levels of complement (all timepoints for both C3 and C4). Table 1 shows the mean C3 and C4 levels in different timepoints according to diagnosis and flare during pregnancy. The lowest levels of complement were observed in patients with a concomitant diagnosis of LN and presence of flare, particularly during the T1 (Figure 1). Nevertheless, both in LN and flare groups the lowest levels of C3 and C4 were documented at T1.

Table 1. Complement levels at the different timepoints according to diagnosis or presence of flare (bold results are statistically significant)

	Patients with LN (237)	Patients without LN (295)	Patients with Flare (170)	Patients without Flare (362)	Patients with LN and Flare (73)	Patients with LN and without Flare (164)
C3 6 months before pregnancy (mean ±SD)	90.7±18.6	94.1±25.2	**85.6±19.1**	**95.6±23.3**	**75 ±17.9**	**99.1±12.5**
C3 conception (mean ±SD)	**96.1±13.9**	**91.1±13**	**95.3±19.5**	**91.8±9.1**	97 ±21.6	95.6±7.1
C3 1st trimester (mean ±SD)	**84.6±32.2**	**98.4±14.1**	**78.3±22.8**	**100.5±20.7**	**56.8 ±19.9**	**97.2±28.7**
C3 2nd trimester (mean ±SD)	108.5±21	108.3±12.2	**94.16±13.4**	**115.7±12.3**	**87.5 ±10.9**	**118.6±16.8**
C3 3rd trimester (mean ±SD)	105.5±15.7	108.2±19.1	**98.97±18.6**	**111.4±16**	**98.1 ±12.6**	**109.1±15.8**
C3 3 months after delivery (mean ±SD)	**93.4±12**	**103.1±15.4**	**92.4±15.7**	**102.6±13.4**	**90.5 ±10.8**	**94.8±12.3**
C4 6 months before pregnancy (mean ±SD)	**15.7±5.5**	**14.1±2.8**	**11.8±3.9**	**16.5±3.3**	**10.5±3.4**	**18.4±4.2**
C4 conception (mean ±SD)	**15.4±4.1**	**13.9±2.8**	**13.3±3.2**	**15.7±3.4**	**11±1.3**	**17.8±3**
C4 1st trimester (mean ±SD)	**15±7.8**	**16.3±2.8**	**12.5±5.9**	**17.5±4.2**	**9.3±7.6**	**17.9±6.2**
C4 2nd trimester (mean ±SD)	**17.7±4.7**	**18.7±4.2**	**15.5±4.3**	**19.8±3.7**	**13.6±4.1**	**19.6±3.5**
C4 3rd trimester (mean ±SD)	17.8±4.4	17.5±5.1	**15.7±5.8**	**18.6±4**	**15.8±4.8**	**18.8±3.9**
C4 3 months after delivery (mean ±SD)	**16.2±4.3**	**19.8±6.9**	**14.9±3.9**	**20±6.4**	**13.3±3.1**	**17.6±4**

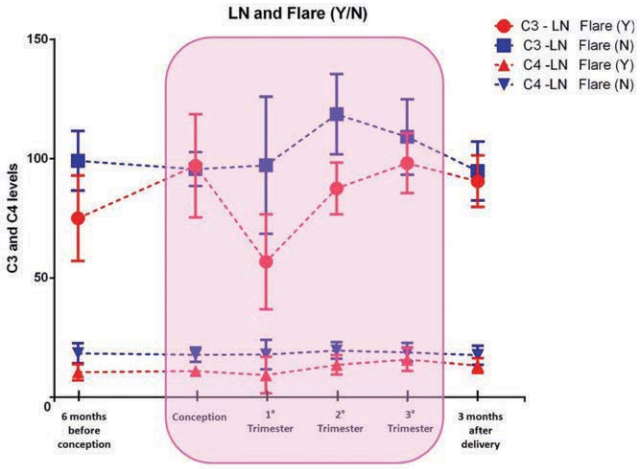

Figure 1. Complement Levels during time in patients with Lupus Nephritis and presence, or absence, of flare.

Conclusion: In this prospective large cohort of SLE patients low C3/C4 levels, particularly in T1, were associated with a higher frequency of flare. Lowering levels of complement, especially in T1, even within normal range might alert the treating clinicians in predicting disease course and consequently avoid flares, especially in LN.

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Breaking the barriers: gut, lung and skin in arthritis pathogenesis

OP0003

DOES IMMUNOSUPPRESSIVE THERAPY IMPROVE GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH SYSTEMIC SCLEROSIS?

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Background: The gastrointestinal (GI) tract is frequently affected in systemic sclerosis (SSc), leading to considerable morbidity and even mortality. While important progress has been made in the last years regarding treatment of SSc, there is no disease-modifying treatment available for SSc-related GI involvement.

Objectives: We aimed to identify, in an observational cohort study of real-life patients with SSc, an association between immunosuppressive therapy and the severity of GI symptoms, measured by the University of California at Los Angeles / Scleroderma Clinical Trial Consortium Gastro-Intestinal Tract instrument 2.0 (UCLA GIT 2.0).

Methods: We selected patients from our EUSTAR centre who met the 2013 ACR/EULAR classification criteria for SSc and had at least two visits with completed UCLA GIT 2.0 questionnaires, with an interval of 12±3 months between visits. We defined the first visit with a completed UCLA GIT 2.0 questionnaire as baseline visit. Immunosuppressive therapy was defined as exposure for at least 6 months between the two visits to at least one of the following drugs, regardless of indication: mycophenolate mofetil (MMF), cyclophosphamide, methotrexate, azathioprine, leflunomide, glucocorticoids (>10mg/d prednisone-equivalent), rituximab, tocilizumab, and abatacept. The study outcome was the UCLA GIT 2.0 score at the follow-up visit. We performed multivariable linear regression with this outcome as dependent variable and immunosuppressive therapy during follow-up, immunosuppressive therapy before baseline, baseline UCLA GIT 2.0 score and several baseline parameters selected by clinical judgment as potentially influencing GI symptoms, as independent variables. Multiple imputation was implemented to handle missing values.

Results: We included 209 patients. Baseline characteristics were: 82.3% female, median (IQR) age 59.0 (48.6, 68.2) years, median disease duration 6.0 (2.7, 12.5) years, 40 (19.1%) diffuse cutaneous SSc, median baseline UCLA GIT 2.0 score 0.19 (0.06, 0.43). Of these, 71 patients were exposed to immunosuppressive therapy during the observation period: 27/71 methotrexate, 1/71 cyclophosphamide, 17/71 MMF, 3/71 leflunomide, 3/71 azathioprine, 6/71 glucocorticoids >10mg/d, 16/34 rituximab, 18/34 tocilizumab. Patients on immunosuppressive therapy during the observation period had, compared to patients without such treatment, overall more severe SSc, higher prevalence of treatment with proton pump inhibitors, similar UCLA GIT 2.0 scores at baseline and at follow up and tendentially less severe GI symptoms at baseline and follow-up by medical history. In multivariable linear regression, immunosuppressive therapy, lower body mass index, longer disease duration and lower baseline UCLA GIT 2.0 score were significantly associated with lower (better) UCLA GIT 2.0 scores at follow-up (Table 1).

Table 1.

Predictors of UCLA GIT 2.0 score at follow-up	*Estimates*	*95% CI*	*p*
Age	0.002	-0.001 – 0.006	0.136
Sex [male]	-0.056	-0.172 – 0.061	0.347
Disease duration	-0.005	-0.009 – -0.000	**0.030**
Body mass index	0.014	0.002 – 0.025	**0.017**
UCLA GIT 2.0 total score baseline	0.690	0.571 – 0.809	**<0.001**
Immunosuppressive therapy during observation period	**-0.119**	**-0.228 – -0.010**	**0.032**
Immunosuppressive therapy before baseline	0.080	-0.032 – 0.192	0.160
Modified Rodnan Skin Score	-0.001	-0.008 – 0.007	0.860
Forced vital capacity	-0.001	-0.004 – 0.001	0.302
Erythrocyte sedimentation rate	0.003	-0.001 – 0.006	0.116
Proton pump inhibitors	-0.034	-0.120 – 0.052	0.435
(Intercept)	-0.120	-0.531 – 0.291	0.566

Baseline factors associated with the total UCLA GIT 2.0 score at the end of the observation period. Multiple linear regression model with imputation for missing variables. N=209 patients

Conclusion: Immunosuppressive treatment was associated with lower UCLA GIT 2.0 scores, which suggests potential effects of immunosuppressants on GI manifestations in patients with SSc. These results need verification in additional studies and randomised controlled clinical trials.

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Complement levels during the first trimester predict disease flare and adverse pregnancy outcomes in systemic lupus erythematosus: A network meta-analysis on 532 pregnancies

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ABSTRACT

Background: Complement levels have been proposed as candidate biomarkers of disease activity and obstetric risk in systemic lupus erythematosus (SLE) pregnancies, but their reliability has been questioned due to the physiologic fluctuations of complement during gestation. Thus, this network meta-analysis aimed at assessing the clinical significance of complement fluctuations in lupus pregnant women.

Methods: Corresponding authors of 19 studies meeting inclusion criteria were invited to contribute with additional data including C3 and C4 levels [before pregnancy, at conception, in every trimester (T) and 3 months after delivery]; data were pooled together in a network meta-analysis.

Results: A total of 532 lupus women from four studies were included in the analysis. In SLE women, C3 and C4 increased progressively during gestation: levels remained stable during T1 and peaked in T2 to decrease in T3. Patients with previous lupus nephritis (LN) and those who experienced flares during pregnancy had significantly lower mean levels of C3 and C4 at all timepoints. The lowest levels of complement were observed, particularly during T1, in patients with LN and gestational flare. Both reduction and the lack of increase of C3 and C4 levels at T1 *versus* conception were associated with gestational flares, particularly in LN patients. Pregnancies with flare had a statistically significant higher rate of maternal and fetal complications(60% versus 50.3%; $p = 0.03$).

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Conclusions: Low complement levels, particularly in T1, were associated with a higher frequency of gestational flare. Either reduction or smaller increase of C3 and/or C4 levels, even within normal range, might predict flares especially in early gestation.

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypical immune complex-mediated disease, characterized by a wide spectrum of clinical phenotypes with heterogeneous courses and progression, varying from persistently low, relapsing-remitting, to persistently high disease activity [1]. The epidemiology of SLE, which mainly presents in young women of childbearing age [2], accounts for the fact that clinicians assist lupus patients very often in their journey towards motherhood. To explain such epidemiological female predominance, several hypotheses have been formulated: candidate risk genes for SLE map on the X chromosome, and estrogens favour autoimmunity by promoting B-cell maturation, antibody production, Th2 responses, and survival of autoreactive cells [3].

As expected, pregnancy can impact SLE disease activity, and in turn SLE may affect obstetric outcomes. Pregnancy in women with SLE has always been regarded as at high risk; however, the significant advancements made in the overall disease management have led to a net improvement of both maternal and fetal outcomes [4,5]. Nevertheless, pregnancy still represents a challenge in women with SLE, especially in those with renal involvement, especially for those with proliferative glomerulonephritis, due to the hazard of disease flare, gestational diabetes and placenta-related disorders, including pre-eclampsia (PE), as well as fetal complications such as miscarriages, fetal loss, intrauterine growth restriction, prematurity, and neonatal lupus [6]. Reliable biomarkers to stratify the risk of a disease flare during pregnancy and to early detect adverse pregnancy outcomes (APO) in pregnant lupus women are still lacking. Complement levels have been proposed as candidate biomarkers of disease activity and of obstetric risk in lupus pregnancies, but their reliability has been questioned due to the physiologic fluctuation of complement levels during gestation [7,8]. Recently, one cohort study described a predictive role of low pre-pregnancy C4 levels towards disease flare during pregnancy [9], while another one found that low-pregnancy C3 levels were associated with preterm birth [10].

In order to optimize the interpretation of available data on the variation of complement levels during SLE pregnancy, we performed a network meta-analysis to assess the fluctuations of C3 and C4 levels from preconception period, throughout pregnancy, and up to 3 months after delivery and to evaluate the association of complement levels with the occurrence of disease flares and/or APO.

2. Patients methods

2.1. Systematic literature review

A detailed literature search strategy has been developed *a priori* to identify articles that reported findings from available prospective

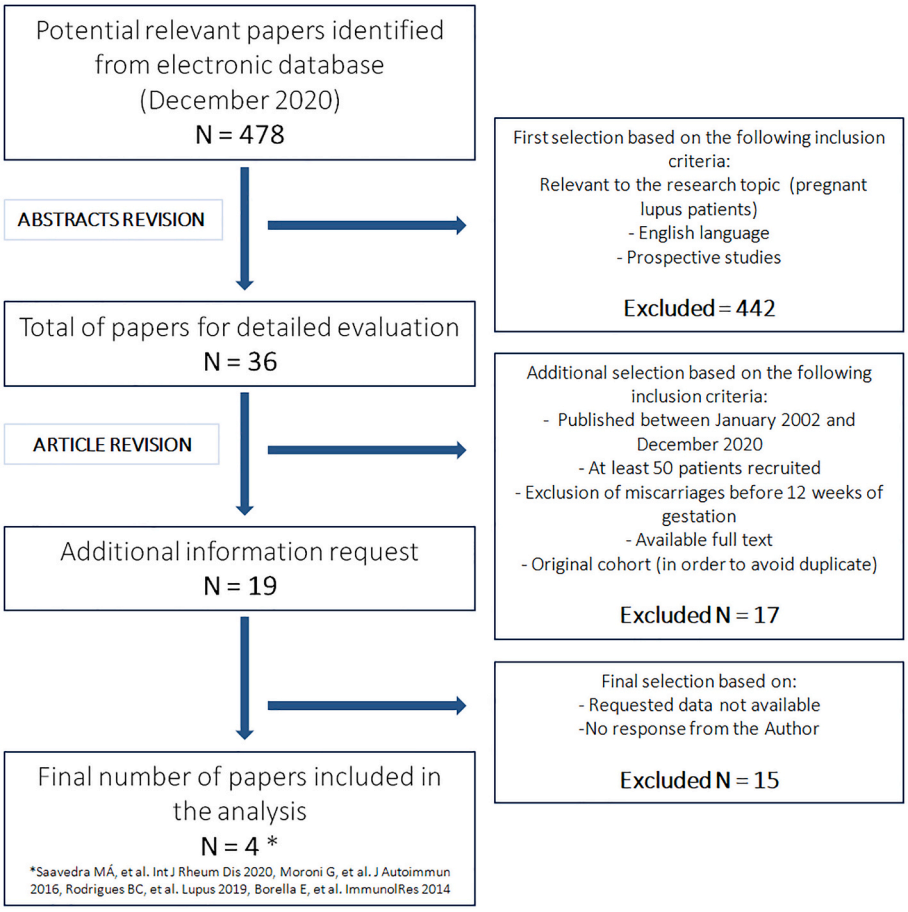

Fig. 1. Literature search strategy.

studies investigating pregnancies in patients with SLE from January 2002 to December 2020. Key words and subject terms included: ((“longitudinal studies”[MeSH Terms] OR (“longitudinal”[All Fields] AND “studies”[All Fields]) OR “longitudinal studies”[All Fields] OR “prospective”[All Fields] OR “prospectively”[All Fields]) AND (“lupus vulgaris”[MeSH Terms] OR (“lupus”[All Fields] AND “vulgaris”[All Fields]) OR “lupus vulgaris”[All Fields] OR “lupus”[All Fields] OR “lupus erythematosus, systemic”[MeSH Terms] OR (“lupus”[All Fields] AND “erythematosus”[All Fields] AND “systemic”[All Fields]) OR “systemic lupus erythematosus”[All Fields]) AND (“pregnancy”[MeSH Terms] OR “pregnancy”[All Fields] OR “pregnancies”[All Fields] OR “pregnancy s”[All Fields])) AND (1000/1/1:2021/6/15[pdat]).

The search strategy was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation from January 2002 to December 2020. Fig. 1 resumes the search strategy.

Retrieved papers were further screened upon additional inclusion criteria in order to refine the search strategy. Inclusion criteria included: a) prospective design, b) a sample size of at least 50 lupus patients, c) exclusion of miscarriages before 12 weeks of gestation as obstetric outcome.

Given the nature of this study, ethics committee approval was not required.

2.2. Data collection and analysis

Two review Authors (M.R. and I.C.) independently assessed studies for inclusion. One review Author completed data extraction, which was checked by a second review Author. A total of 19 studies were finally selected for data request. Each corresponding Author of the selected manuscripts was invited to contribute with additional data of individual pregnancies that were not presented in the published manuscript, including complement levels, C3 and C4 separately, at 6 months before pregnancy, at conception, during the first trimester (T1), during the second trimester (T2), during the third trimester (T3), and 3 months after delivery (post-partum, PP). Further details on the number of pregnancies, patients’ classification, diagnosis at conception, treatment during pregnancy, occurrence of flares during gestation, as well as maternal and fetal outcomes were also recorded. We performed a network meta-analysis within a Bayesian framework as previously described [11].

2.3. Statistical analysis

Categorical variables are presented as numbers (%) and continuous variables are expressed as mean ± standard deviation (SD). The significance of baseline differences was determined by the chi-squared test, Fisher’s exact test or the unpaired *t*-test, as appropriate. Correlation analysis, linear regression, and Odds Ratio (OR) were also performed. Missing data were approached with mean substitution system. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA).

2.4. Study variables definitions

SLE, lupus nephritis (LN), and antiphospholipid syndrome (APS) diagnosis and classification were based upon each study definition [12–14]. SLE flare was defined by the need of new immunosuppressive therapy or increase in the dosage of prednisone $\geq$10 mg/day.

APO were defined as follows:

a) fetal death after 12 weeks’ gestation in the absence of chromosomal abnormalities, anatomic malformations, or congenital infections;
b) neonatal death before hospital discharge due to complications related to prematurity or placental insufficiency (*e.g.*, abnormal fetal surveillance test results, abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, or oligohydramnios, or both);
c) preterm delivery or pregnancy loss at $<$36 weeks due to gestational hypertension, PE, or placental insufficiency;
d) small for gestational-age neonate, defined as one with a birth weight below the 5th percentile without anatomical or chromosomal abnormalities.

The fluctuation of C3 and C4 levels between T1 and conception was defined as $\Delta C3_{T1\text{-conception}}$ and $\Delta C4_{T1\text{-conception}}$. When the decrease in C3 levels between T1 and conception was below 2 mg/dl or the increase in C3 at T1 *versus* conception was below 4 mg/dl (defined using two standard deviations from mean, as per Westgard rules), $\Delta C3_{T1\text{–conception}}$ was considered as clinically not relevant.

3. Results

3.1. C3 and C4 levels progressively increased during gestation in women with SLE

A total of 532 SLE women from 4 studies were included in the analysis [15–18]. APS had been diagnosed in 68 women (12.8%), while 82 patients (15.4%) were positive for antiphospholipid antibodies (aPL) without overt clinical manifestations of APS (referred as “aPL carriers”). As detailed in Table 1 and visually presented in Fig. 2A, both C3 and C4 levels increased progressively in women with SLE during gestation. In particular, C3 and C4 levels remained stable during T1 and peaked at T2, then decreased during T3. At 3 months after delivery, a different behavior was noted for C3 and C4: C3 continued to decrease whereas C4 levels in the PP period were higher than those registered in T3.

3.2. Patients with flares during pregnancy displayed significantly lower levels of complement compared to patients without gestational flare

A flare during pregnancy was observed in 170 patients (32%). Levels of both C3 and C4 were lower at all timepoints in subjects who experienced flares during pregnancy (C3 at T1 78.3 ± 22.8 *versus* 100.5 ± 20.7, $p < 0.001$; C3 at T2 94.2 ± 13.4 *versus* 115.7 ± 12.3, $p < 0.001$; C3 at T3 99 ± 18.6 *versus* 111.4 ± 16, $p < 0.001$; C3 at PP 92.4 ± 15.7 *versus* 102.6 ± 13.4, $p < 0.001$; Table 1 and Fig. 2B).

The physiological increase in complement levels throughout gestation was rather marked among patients who did not experience a disease flare while pregnant. Complete data on complement levels fluctuation at all time-points in patients experiencing a gestational flare *versus* those who did not present a disease flare while pregnant are listed in Table 1 and illustrated in Fig. 2B.

3.3. Patients with LN displayed significantly lower levels of complement compared to patients without renal involvement

LN had been diagnosed in 237 women (44.5%). Patients with LN had significantly lower levels of complement when compared to patients without renal involvement (C3 at T1 84.6 ± 32.2 *versus* 98.4 ± 14.1, $p < 0.001$; C3 at PP 93.4 ± 12 *versus* 103.1 ± 15.4, $p < 0.001$; C4 at T1 15 ± 7.8 *versus* 16.3 ± 2.8, $p < 0.001$; C4 at PP 16.2 ± 4.3 *versus* 19.8 ± 6.9, $p < 0.001$, Table 1and Fig. 2C).

3.4. Patients with previous LN and flare during pregnancy displayed the lowest complement levels

A flare during pregnancy was observed in 73 women with a previous diagnosis of LN. The lowest levels of complement, both for C3 and C4, were observed in patients with a previous diagnosis of LN who experienced a flare during pregnancy. Complete data are listed in Table 1 and visually represented in Fig. 2C.

Table 1
Complement levels at the six different timepoints (values expressed as mean ± SD), according to diagnosis of lupus nephritis (LN) or presence of a disease flare during pregnancy.

	All SLE patients (*N* = 532)	Patients with LN (*N* = 237)	Patients without LN (*N* = 295)	Patients with flare (*N* = 170)	Patients without flare (*N* = 362)	Patients with LN and flare (*N* = 73)	Patients with LN and without flare (*N* = 164)
C3 6 months before pregnancy	92.3 ± 22.9	90.7 ± 18.6	94.1 ± 25.2	**85.6 ± 19.1**	**95.6 ± 23.3**	**75 ± 17.9**	**99.1 ± 12.5**
C3 at conception	92.4 ± 14.4	**96.1 ± 13.9**	**91.1 ± 13**	**95.3 ± 19.5**	**91.8 ± 9.1**	97 ± 21.6	95.6 ± 7.1
C3 T1	92.9 ± 23.8	**84.6 ± 32.2**	**98.4 ± 14.1**	**78.3 ± 22.8**	**100.5 ± 20.7**	**56.8 ± 19.9**	**97.2 ± 28.7**
C3 T2	107.8 ± 16.9	108.5 ± 21	108.3 ± 12.2	**94.16 ± 13.4**	**115.7 ± 12.3**	**87.5 ± 10.9**	**118.6 ± 16.8**
C3 T3	106.9 ± 18.1	105.5 ± 15.7	108.2 ± 19.1	**98.97 ± 18.6**	**111.4 ± 16**	**98.1 ± 12.6**	**109.1 ± 15.8**
C3 3 months PP	99.1 ± 14.9	**93.4 ± 12**	**103.1 ± 15.4**	**92.4 ± 15.7**	**102.6 ± 13.4**	**90.5 ± 10.8**	**94.8 ± 12.3**
C4 6 months before pregnancy	14.7 ± 4.2	**15.7 ± 5.5**	**14.1 ± 2.8**	**11.8 ± 3.9**	**16.5 ± 3.3**	**10.5 ± 3.4**	**18.4 ± 4.2**
C4 at conception	14.4 ± 3.5	**15.4 ± 4.1**	**13.9 ± 2.8**	**13.3 ± 3.2**	**15.7 ± 3.4**	**11 ± 1.3**	**17.8 ± 3**
C4 T1	15.8 ± 5.3	**15 ± 7.8**	**16.3 ± 2.8**	**12.5 ± 5.9**	**17.5 ± 4.2**	**9.3 ± 7.6**	**17.9 ± 6.2**
C4 T2	18.3 ± 4.4	**17.7 ± 4.7**	**18.7 ± 4.2**	**15.5 ± 4.3**	**19.8 ± 3.7**	**13.6 ± 4.1**	**19.6 ± 3.5**
C4 T3	17.6 ± 4.9	17.8 ± 4.4	17.5 ± 5.1	**15.7 ± 5.8**	**18.6 ± 4**	**15.8 ± 4.8**	**18.8 ± 3.9**
C4 3 months PP	18.3 ± 6.2	**16.2 ± 4.3**	**19.8 ± 6.9**	**14.9 ± 3.9**	**20 ± 6.4**	**13.3 ± 3.1**	**17.6 ± 4**
ΔC3(ΔC3 T1– at conception)	10.3 ± 43.2	**0.5 ± 53.2**	**16.6 ± 34.3**	**−6.7 ± 48.8**	**18.8 ± 37.6**	**−36.1 ± 42.6**	**17.3 ± 49.1**
ΔC4 (ΔC4 T1– at conception)	3.4 ± 7.6	**1.5 ± 9.1**	**4.5 ± 6.3**	**1.2 ± 8.1**	**4.4 ± 7.1**	**−1.1 ± 8.5**	**2.8 ± 9.1**

Results highlighted in bold are statistically significant.
Abbreviations: SLE, systemic lupus erythematosus; LN, lupus nephritis; T1, 1st trimester of gestation; T2, 2nd trimester of gestation, T3, 3rd trimester of gestation; PP, post-partum period (up to 3 months after delivery).

3.5. The fluctuations of C3 and C4 levels at T1 versus conception displayed the highest clinical significance in predicting disease flares

When analyzing the fluctuations of complement levels between different timepoints, the variations in both C3 and C4 between levels assessed at T1 *versus* those recorded at conception emerged as the most clinically significant. Indeed, the differential values in both C3 and C4 at T1 *versus* at conception (defined as $\Delta C3_{T1-conception}$ and $\Delta C4_{T1-conception}$, respectively) were significantly lower in patients with LN when compared to patients without renal involvement (ΔC3 0.5 ± 53 *versus* 16.6 ± 34.3, $p < 0.001$; ΔC4 1.5 ± 9.1 *versus* 4.5 ± 6.3, $p < 0.001$).

Women who experienced a flare during pregnancy had lower $\Delta C3_{T1-conception}$ and $\Delta C4_{T1-conception}$ ($\Delta C3_{T1-conception}$ − 6.7 ± 48.8 *versus* 18.8 ± 37.6, $p < 0.001$; ΔC4 1.2 ± 8.1 *versus* 4.4 ± 7.1, $p < 0.001$). The lowest levels of $\Delta C3_{T1-conception}$ and $\Delta C4_{T1-conception}$ were reported in patients that were diagnosed with LN and experienced flares during pregnancy ($\Delta C3_{T1-conception}$ − 36.1 ± 42.6; $\Delta C_{T1-conception}$ − 1.1 ± 8.5).

A decrease in $\Delta C3_{T1-conception}$ yielded an OR for flare during pregnancy of 3.1 (CI 95% 2.1–4.8) when below 5 mg/dL, an OR that increased up to 3.9 (CI 95% 2.5–6) when below 15 mg/dL.

Similar figures emerged when assessing the association between $\Delta C3_{T1-conception}$ and a prior diagnosis of LN: $\Delta C3_{T1-conception} \leq 5$ mg/dL conveyed an OR for a prior diagnosis of LN of 6.1 (CI 95% 3.9–9.6) while $\Delta C3_{T1-conception} \leq 10$ mg/dL conveyed an OR of 7.2 (CI 95% 4.5–11.7). Interestingly, even the lack of clinically relevant changes in the complement levels between T1 and conception was associated with both previous LN diagnosis (OR 2.2; CI 95% 1.3–3.6) and development of flare during pregnancy (OR 5.2; CI 95% 2.9–9.3). Table 2 resumes the results of the coefficient of risk conveyed by different $\Delta C3_{T1-conception}$ levels upon LN diagnosis or presence of flare.

3.6. The fluctuations of C3 and C4 levels at T1 versus conception displayed the highest clinical significance in predicting APO

Preterm delivery or miscarriage at <36 weeks were more frequent in women with a previous diagnosis of APS (39.7% *versus* 23%; $p = 0.003$), in patients who developed flares during pregnancy irrespectively of a concomitant diagnosis of LN (42.5% *versus* 28%; $p = 0.01$ in patients with LN and 34% *versus* 17.2%; $p = 0.01$ in those without a diagnosis of LN). Additionally, fetal death was more frequent in patients with a diagnosis of LN and positive aPL (4 out of 30 versus 6 out of 206; $p = 0.008$).

When computing all APO together, higher rates of complications were reported in patients with a previous diagnosis of APS (88.2% *versus* 56%; $p < 0.0001$) as well as LN (67.9% *versus* 53.9%; $p < 0.0001$) and occurrence of flare during pregnancy (91.2% *versus* 45.6%; $p < 0.0001$).

$\Delta C3_{T1-conception} \leq 5$ mg/dL and no changes of $\Delta C3_{T1-conception}$ were both associated with higher rates of overall APO (63.4% *versus* 45.6%; $p = 0.003$ and 58.5% *versus* 72.8%; $p = 0.02$, respectively).

4. Discussion

The present network meta-analysis, which includes more than 500 pregnant lupus patients from 4 international independent studies, allowed us to clearly assess the clinical relevance of complement monitoring during gestation to predict both disease flares and APO. Levels of C3 and C4 emerged as reliable biomarkers to identify those women who are at higher risk of developing disease flares and APO, even in case of a concomitant diagnosis of LN [19]. These findings are extremely relevant from a clinical perspective given that, despite the substantial improvements accomplished in the management of SLE patients, 50% of lupus women might develop a flare during gestation, with severe organ involvement occurring in up to 25% of cases [20,21]. Unfortunately, the current lack of reliable biomarkers and validated tools for the assessment of disease activity during pregnancy limits our ability to predict which subjects will experience disease worsening and/or APO. In the last few decades, several scoring systems have been developed to assess lupus activity and the risk of flare during pregnancy. Most of these tools, such as the LAI in Pregnancy (LAI-P), the SLE-Pregnancy Disease Activity Index (SLEPDAI), and the modified SLAM3 (m-SLAM) [22], include hypocomplementemia (C3 and C4). These clinimetric instruments have been created by modifying existing lupus activity indexes in order to differentiate between disease-specific features and physiologic changes occurring during gestation. Although promising, these pregnancy-adapted scores have not been extensively validated in large prospective cohorts and therefore their current employment in clinical practice is strongly limited. Similarly, C3 and C4 levels should be carefully evaluated in pregnant lupus women as complement serum levels rise throughout the course of normal gestation

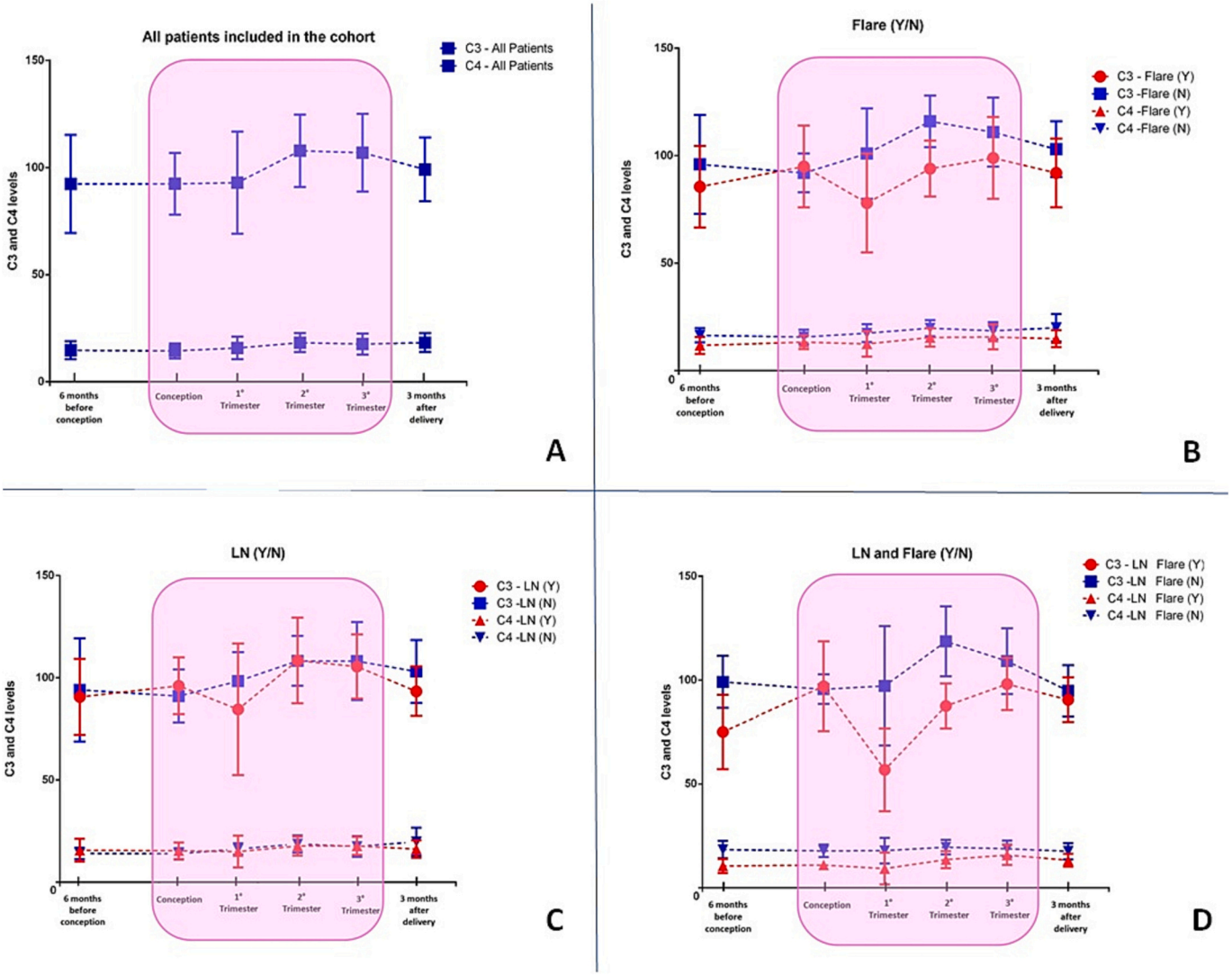

Fig. 2. Complement levels fluctuations over 6 time points (before conception, at conception, during each trimester of pregnancy, and after delivery).
Panel 2A. Linear representation of the complement levels overtime in the entire cohort of systemic lupus erythematosus patients (SLE). **Panel 2B.** Linear representation of the fluctuations of complement levels during pregnancy in patients with SLE with and without the occurrence of flares during pregnancy. **Panel 2C.** Linear representation of complement levels during time in patients with and without lupus nephritis (LN). **Panel 2D.** Linear representation of complement levels during time in patients with and without LN and presence, or absence, of flare during pregnancy.

[23]. This study confirms that complement levels fluctuate over the gestational course also in SLE women: values of C3 and C4 remained stable at early stages of pregnancy, then progressively increased during the second trimester of gestation; once reached the highest levels, both C3 and C4 showed a decline with discrepant behaviors after delivery, resulting in a constant rise of C4 values and a progressive decrease of C3. Interestingly, we observed that lupus patients who experienced a clinical flare during pregnancy had significantly lower mean values of C3 and C4 throughout the entire gestation compared with patients with stable disease activity. If our data confirm the relevance of complement as a monitoring tool of lupus disease activity even during gestation, it should be mentioned that the consensus about the reliability of complement in predicting SLE flare is not unanimous. Indeed, its relevance has been questioned by few studies [24–27], most likely due to the methodological challenges of accurately measuring circulating complement levels as well as to the inappropriate designs of clinical studies [28]. Nevertheless, despite these inconsistencies, it is universally accepted that complement activation in SLE is mirrored by a secondary decline of circulating complement levels and a parallel increase in complement split products and circulating levels of complement proteins (C3 and C4) are extensively used in clinical practice for classification and diagnostic purposes, monitoring of disease activity and follow-up. Similarly, the clinical significance of low C3 and C4 circulating levels as biomarkers for LN is still matter of research [29]. Whereas a significant drop in C4 levels can be observed even two months prior to renal flare occurrence, a decline in C3 was shown to be influenced by genetic variants of factor H, which regulates C3-convertase in the alternative pathway [30]. In addition, elevated titers of autoantibodies directed against C1q have been described as better predictors of renal involvement in SLE patients compared to C3 and C4, although with inconclusive results [30]. Further analysis of our data revealed significantly lower levels of C3 and C4 in pregnant patients with flare at all time-points considered, from conception throughout pregnancy and until 3 months following delivery, consistently with what reported by other authors [30]. Most importantly, the present study also highlights that those patients with both previous LN and disease flare during gestation had the lowest complement levels, suggesting that levels of C3 and C4 below the normal threshold before conception can serve as predictor of flare during pregnancy in this high-risk group of patients [31].

To better evaluate the fluctuations of C3 and C4 by minimizing the

Table 2
Odds Ratios (OR) according to lupus nephritis (LN) diagnosis or presence of flare and different ΔC3 levels (first trimester –at conception).

	FLARE OR	FLARE CI 95%	LN OR	LN CI 95%	LN & FLARE OR	LN & FLARE CI 95%
ΔC3 ≥ 15 mg/dL	0.3	0.2–0.5	1.2	0.7–2.5	0.06	0.02–0.3
ΔC3 ≥ 10 mg/dL	0.5	0.3–0.7	0.4	0.3–0.5	0.03	0.01–0.1
ΔC3 ≥ 5 mg/dL	0.4	0.3–0.6	0.2	0.1–0.3	0.02	0.01–0.07
ΔC3 no change defined as [−2;+4] mg/dL	1.1	0.6–1.9	**2.2**	**1.3–3.6**	**5.2**	**2.9–9.3**
ΔC3 ≤ 5 mg/dL	**3.1**	**2.1–4.8**	**6.1**	**3.9–9.6**	**6.5**	**3.9–11.2**
ΔC3 ≤ 10 mg/dL	**3.3**	**2.2–5.1**	**7.2**	**4.5–11.7**	**5.6**	**3.3–9.7**
ΔC3 ≤ 15 mg/dL	**3.9**	**2.5–6**	**6.4**	**4–10.3**	**6.2**	**3.6–10.7**

Results highlighted in bold are statistically significant.

confounding effect of cut-off variability and inter-assay heterogeneity among the four different cohorts, as well as the potential influence of genetic variants, the analysis in this network meta-analysis also focused on the differential levels of circulating C3 and C4 values (ΔC3 and ΔC4) between different trimesters of gestation, rather than the mere absolute levels or the dichotomous categorization into hypocomplementemia *versus* normocomplementemia. This approach allowed us to determine that the most informative data in clinical practice consists in the lack of physiological increase in C3 and C4 values in the first trimester of gestation as compared to conception: women who experienced a lupus flare during gestation displayed the lowest ΔC3 and ΔC4 during the first trimester *versus* at conception. In addition, the less pronounced the increase in C3 levels is from conception throughout the first trimester of gestation, the higher the risk of developing disease flare with an OR up to 3.9 when ΔC3 is below 15 mg/dl. The same conclusion can be extrapolated to pregnant women with renal involvement and the occurrence of flare during gestation, a subset of patients in which a small ΔC3 carried an even higher risk of disease flare (OR 5.2). Despite the significance of C4 variations during pregnancy in predicting both APO and disease flare, we decided to emphasize the results obtained when focusing on C3 variations. In fact, from a practical point of view, and based on the more extended range of C3 values, ΔC3 might be easier to assess and more informative for clinicians.

The data gathered in this meta-analysis allowed us to investigate also the role of complement levels in predicting obstetric morbidity among lupus women. Women with lower levels of both C3 and C4 prior to conception and during the entire gestation are more likely to experience APO: a ΔC3 below 5 mg/dl between the first trimester and at conception as well as no changes in ΔC3 at these time-points were associated with an overall higher rate of APO. These findings are consistent with the available literature, which traditionally enlists hypocomplementemia, together with active LN at conception, previous history of LN, aPL positivity and high disease activity before conception, as major determinants of poor maternal and fetal outcomes in lupus women [6].The relationship between complement levels and APO should not be surprising, given the multifaceted role of the complement cascade in pregnant lupus women. On one hand, the complement system, with more than30 plasma proteins and receptors, represents a key element of the innate immunity response that contributes to the progression of SLE through the stimulation of inflammation and the removal of immune complexes, cells, and apoptotic debris [32]. Importantly, SLE onset, disease activity and organ damage have been all linked to complement activation and consumption, as well as to complement deficiencies [33]. On the other hand, a consistent stream of data has progressively shown that the complement cascade exerts a pivotal role throughout all the stages of physiologic gestation (conception, embryo implantation, placentation, fetal growth, and labor) and the fine tuning of the expression of complement factors, receptors and inhibitors during gestation, with their increased hepatic synthesis, is mandatory to ensure a successful pregnancy [34].

This study presents some limitations that should be acknowledged. First, the limited number of included studies does not encompass the whole prospective experience in lupus pregnancy available in the literature. Second, the geopolitical representation of the included cohorts does not comprehend North America, Asia-Pacific and Africa, thus reducing the generalizability of our conclusions. Third, since SLE is an extremely heterogeneous condition, the inclusion of patients with distinct clinical profile might limit the reproducibility of the observed results. Fourth, given the nature of the study, the lack of a control group (*e.g.* healthy subjects) represents another limitation. Despite the acknowledged limitations, our study has indeed some strengths: the high number of included patients, the prospective design of the considered studies, and lupus diagnosis assessed with homogeneous criteria across different cohorts [12–14]. Moreover, despite the absence of complement levels adjustment for gestational state or trimester [35], cut-off values for circulating levels C3 and C4 were comparable among different cohorts.

This network meta-analysis suggests the role of C3 and C4 levels/fluctuations before conception and in early pregnancy as predictors of SLE flares and APO later in the pregnancy course. Particularly, the lack of increase in C3 and C4 levels during the first 13 weeks of gestation appeared as a strong predictor of flare, especially in women with previous LN. These findings deserve further validation in order to define the role of complement as a biomarker that can inform risk stratification and guide individualized treatment decisions in women with SLE who are pregnant or planning to get pregnant.

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Patients and public involvement statement

Patients were not involved in this study.

CRediT authorship contribution statement

Massimo Radin: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Irene Cecchi:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Francesca Crisafulli:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Evandro Mendes Klumb:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Guilherme Ramires de Jesús:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Marcela Ignacchiti Lacerda:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Miguel Ángel Saavedra:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Geraldine Vanessa Reyes-Navarro:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Luca Iaccarino:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Maddalena Larosa:** Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Gabriella Moroni:** Data curation, Investigation, Methodology,

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Declaration of Competing Interest

None declared.

Data availability

Data will be available upon reasonable request.

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Low Preconception Complement Levels Are Associated with Adverse Pregnancy Outcomes in a Multicenter Study of 260 Pregnancies in 197 Women with Antiphospholipid Syndrome or Carriers of Antiphospholipid Antibodies

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Abstract: Antiphospholipid antibodies (aPL) can induce fetal loss in experimental animal models. Human studies did find hypocomplementemia associated with pregnancy complications in patients

with antiphospholipid syndrome (APS), but these results are not unanimously confirmed. To investigate if the detection of low C3/C4 could be considered a risk factor for adverse pregnancy outcomes (APO) in APS and aPL carriers' pregnancies we performed a multicenter study including 503 pregnancies from 11 Italian and 1 Russian centers. Data in women with APS and asymptomatic carriers with persistently positive aPL and preconception complement levels were available for 260 pregnancies. In pregnancies with low preconception C3/C4, a significantly higher prevalence of pregnancy losses was observed ($p = 0.008$). A subgroup analysis focusing on triple aPL-positive patients found that preconception low C3 and/or C4 levels were associated with an increased rate of pregnancy loss ($p = 0.05$). Our findings confirm that decreased complement levels before pregnancy are associated with increased risk of APO. This has been seen only in women with triple aPL positivity, indeed single or double positivity does not show this trend. Complement levels are cheap and easy to be measured therefore they could represent a useful aid to identify patients at increased risk of pregnancy loss.

Keywords: pregnancy; complement; antiphospholipid antibodies; antiphospholipid syndrome; gestational outcome

1. Introduction

Antiphospholipid syndrome is a rare autoimmune disease characterized by thrombotic events involving the venous and arterial systems, including microcirculation, and/or pregnancy morbidities in the presence of confirmed positivity for aPL [1]. aPL are mainly directed against phospholipid-binding proteins and the main antigenic target for aPL is beta2glycoprotein I (B2GPI), a protein found on lipid layers in cellular membranes [2]. The complement system has attracted attention as a potential mediator of pathogenic mechanisms induced by aPL and its activation is regarded as a necessary event not only for thrombosis but also for obstetric complications [3,4]. The complement system comprises over 30 proteins that act in concert to protect the host against invading organisms. Its activation can be triggered via three different pathways: classical, alternative, and leptin. All the pathways converge on the C3 protein and cleave to generate fragments C3a and C3b. C3b attaches covalently to targets, followed by assembly of C5 convertase and the subsequent cleavage of C5 to C5a and C5b [5]. Since the mid-1990s, it has been investigated that activated complement fragments have the capacity to bind and activate inflammatory and endothelial cells in vivo, as well as to induce a prothrombotic phenotype. Several mechanisms have been proposed to account for aPL-induced activation of complement. In particular, anti-B2GPI antibodies-B2GPI complexes have been shown to activate the complement cascade.

In obstetric APS, evidence of complement role has been gained in animals treated with aPL fractions. Girardi et al. demonstrated that C5 deficiency or treatment of mice with anti-C5a monoclonal antibody protects against aPL-induced pregnancy loss and growth retardation [3]. Another group in the same year published that inhibition of the complement cascade in vivo using the C3 convertase inhibitor (Crry-Ig) prevents fetal loss and growth restriction [6]. Furthermore, mice deficient in C3, C4, C5, and factor B were not prone to develop aPL-induced fetal loss [7–9]. The progressive evidence of complement involvement in aPL-related pregnancy loss derived by animal models prompted several groups to investigate the significance of complement levels in human disease. B2GPI, the recognized main target of aPL, is widely represented on trophoblast and decidual surface [10]. Complement C3 and C4 serum levels were then assessed in several cohorts of pregnant patients with APS and/or aPL in order to relate complement consumption with APO. However, these studies have yielded inconsistent results, in fact, while some studies have come to find a correlation [11,12], other studies have not revealed a prognostic role for the complement in relation to pregnancy morbidity among aPL-positive

women [13,14]. More recently, complement activation products were found to be increased during pregnancy in patients with aPL and APO by two different groups [15,16].

This multicenter retrospective study was conducted to further clarify the prognostic role of preconception serum C3 and C4 levels in a cohort of APS and/or aPL carrier pregnant women without any underlying autoimmune disease.

2. Materials and Methods

2.1. Study Cohort and Inclusion/Exclusion Criteria

Medical records of pregnant women with confirmed positivity for aPL antibodies attending twelve referral centers from January 2010 to December 2020 were retrospectively evaluated.

Exclusion criteria were the presence of an associated systemic autoimmune disease, diagnosed according to the international classification criteria, voluntary termination of pregnancy, fetal losses due to severe fetal malformations. Demographic and clinical data were collected in an anonymized ad hoc created database:

- criteria and non-criteria manifestations of APS [1];
- aPL profile and C3 and C4 levels at diagnosis and preconception (considered at least 6 months before pregnancy);
- therapy during the three trimesters of pregnancy;
- gestational outcome and maternal complications.

2.2. APO Definitions

For the purpose of this study, we considered as aPL-related APO: spontaneous abortions (<10 weeks of gestation), fetal loss (≥10 weeks of gestation), neonatal death (death of a formed fetus alive at birth in the first 28 days of life), preterm delivery before 37 weeks of gestation, preeclampsia, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet). We excluded pregnancies with other recognized causes for adverse pregnancy outcomes (i.e., therapeutical abortion consequent to the finding of anatomical abnormalities).

2.3. Autoantibody Detection

aPL were tested by each participating center in a referral laboratory. Anticardiolipin antibodies (aCL) and antiB2GPI antibodies (aB2GPI) were detected by ELISA according to the current recommendations [17]. Lupus anticoagulant (LA) was detected by coagulation assay according to the guidelines of the International Society on Thrombosis and Hemostasis [18]. Complement C3 and C4 fractions were detected as in clinical practice.

2.4. Statistical Analysis

Categorical variables were reported as a proportion and/or percentage, whereas continuous variables as mean (±standard deviation) values. Fisher's exact test or chi-squared test for categorical variables and Mann–Whitney test for continuous variables were applied as appropriate. All tests were performed using GraphPad Prism 9. Logistic regression was applied for multivariate analysis using Statview. p-values ≤ 0.05 were considered significant and odds ratio (OR) with 95% confidence interval (95% CI) was indicated.

3. Results

We collected data about 503 pregnancies in 383 patients. The patients were Caucasian (n = 342, 89.2%), African Americans (n = 21, 5.5%), Asian (n = 14, 3.7%), and Latin American (n = 6, 1.6%). In 333 patients (86.9%), a diagnosis of APS according to the classification criteria [1] had been formulated, while 50 (13.1%) were aPL carriers.

Most of the women (228, 68.5%) presented with obstetric morbidity only, while 105 patients (31.5%) had experienced thrombotic events, with or without pregnancy morbidity.

In this cohort, 260 singleton pregnancies in 197 patients with available preconception complement levels and gestational outcomes (52%), 76/143 aPL carriers (53%), and 184/360 (51%) APS pregnancies, were available. A total of 93 (36%) of all pregnancies had

low levels of preconception C3 (51/93, 55%) or C4 (13/93, 14%) or both (29/93, 31%). A total of 167 (64%) pregnancies had normal complement levels.

3.1. Autoantibodies Profile

The results of the three aPL assays were available for all the patients. LA was detectable in 97 pregnancies (37.3%). aCL IgG were positive in 180 pregnancies (69.2%), and IgM in 77 (29.6%); anti-B2GPI IgG antibodies were positive in 110 pregnancies (42.3%) and IgM in 96 (36.9%). A triple aPL positivity was observed in 62 women (23.8%) while double in 55 (21.2%) and single in 143 (55%). Antinuclear antibodies (ANA) were persistently positive in 71 patients (27%), anti-dsDNA in 8 (8.6%), anti-extractable nuclear antigens (anti-ENA) in 9 (3.5%), and anti-thyroperoxidase antibody (anti-TPO) and/or anti-thyroglobulin antibody (anti-TG) in 24 (9.2%).

3.2. Pregnancy Outcome

Most pregnancies (224, 86.2%) culminated with a live birth, at a mean gestational age of 37.6 ± 3.4 weeks (range 25.6–41.5). As detailed in Table 1, pregnancy loss occurred in 36 gestations.

Table 1. Outcome and APO of the study cohort.

Gestational Outcome and Maternal Complications	260 Pregnancies (N, %)
Spontaneous abortion	27 (10.4%)
Fetal death	7 (2.7%)
Live births	224 (86.2%)
Neonatal death	2 (0.8%)
Preterm deliveries < 37 weeks	77 (29.6%)
SGA [a]	3 (1.2)
Intrauterine growth restriction	5 (1.9)
Preeclampsia/HELLP syndrome [b]	14 (3.9)
Thrombocytopenia	6 (2.3)
DVT [c]	3 (1.1)
Gestational diabetes	6 (2.3)
PROM [d]	9 (3.5)
Hemolytic anemia	1 (0.4)

[a] SGA: small for gestational age was defined as a birth weight in the <10th percentile for gestational age. [b] HELLP syndrome: concomitant presence of severe thrombocytopenia (platelets ≤ 50,000/μL), evidence of hepatic dysfunction (liver enzymes ≥70 IU/l), and evidence suggestive of hemolysis (total serum lactate dehydrogenase ≥600 IU/l). [c] DVT: deep vein thrombosis. [d] PROM: preterm premature rupture of membranes was defined as rupture of the membranes before 37 weeks of gestation.

During follow-up APO were described in 94 APS and 21 aPL carriers' pregnancies (51% and 29% respectively). Patients with APO showed significant lower complement levels than women with uncomplicated pregnancies (Figure 1).

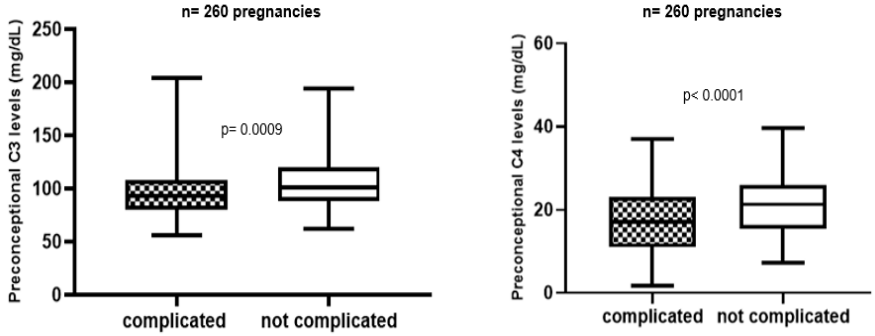

Figure 1. Preconception complement level in complicated vs. not complicated pregnancies.

Considering the 93 patients (71 APS and 22 aPL carriers) with low preconception C3 and/or C4 and comparing them to patients with normal complement level, a significantly higher prevalence of pregnancy losses was observed ($p = 0.008$) as well as a higher prevalence of preterm live birth from the 37th week of gestation and earlier (Table 2).

Table 2. Relationship between gestational outcome, maternal pregnancy complications and preconception complement levels.

	All Pregnancies (n = 260)				Triple aPL Positivity (n = 62)				Single or Double aPL Positivity (n = 198)			
Gestational Outcome	**Low C3/C4 (n = 93)**	**Normal C3/C4 (n = 167)**	***p***	**OR (CI 95%)**	**Low C3/C4 (n = 48)**	**Normal C3/C4 (n = 14)**	***p***	**OR (CI 95%)**	**Low C3/C4 (n = 45)**	**Normal C3/C4 (n = 153)**	***p***	**OR (CI 95%)**
Term live birth (≥37 w)	39 (42%)	121 (72%)	<0.0001	0.367 (0.205–0.655)	13 (27%)	7 (50%)	ns	-	26 (58%)	114 (75%)	ns	-
Preterm live birth (<37 w)	34 (37%)	30 (18%)	<0.0001	2.390 (1.337–4.274)	23 (48%)	7 (50%)	ns	-	11 (24%)	23 (15%)	ns	-
Pregnancy losses (abortion, fetal death, and neonatal death)	20 (21%)	16 (10%)	0.008	2.586 (1.266–5.282)	12 (25%)	0 (0%)	0.05	-	8 (18%)	16 (10%)	ns	-

Furthermore, we performed subgroup analysis, considering separately patients with triple aPL positivity. It is worthwhile to underline that in these 62 patients decreased C3/C4 were extremely common (77.4%). In this group of high-risk patients, preconception low C3 and/or C4 levels were found to be associated with an increased rate of pregnancy loss ($p = 0.05$). On the other hand, among women with single or double aPL positivity, APO was not related to preconception complement levels (Table 2). Maternal complications (preeclampsia n = 14, deep vein thrombosis n = 3, and thrombocytopenia n = 6) were not statistically related with low preconception levels of C3 and/or C4.

In multivariate analysis, the only feature associated with complicated pregnancies was the preconception triple positivity for aPL, both in APS and aPL carrier group ($p = 0.02$, OR 2.421, CI 95% 1.112–5.273 and $p = 0.03$, OR 5.823, CI 95% 1.120–30.277, respectively). C3 and C4 preconception levels did not show any correlation, as well as maternal diagnosis.

3.3. Treatment

Most patients with APS were treated with low-dose-aspirin (LDA, n = 161; 87.5%) and/or low-molecular-weight heparin (LMWH; n = 158; 85.8%) during pregnancy. Immunomodulatory or immunosuppressive therapy was recorded in 40 pregnancies, with hydroxychloroquine (HCQ) administrated in 38 cases (20.6%) and low-dose corticosteroids (CS) in 8 (4.3%).

Pregnancies in aPL carriers were treated with LDA in 64 cases (84.2%) and LDA and/or LMWH in 28 (26.8%). In these patients, HCQ was administrated in 4 (5.2%) pregnancies and CS in 5 (6.5%).

Combination therapy with LDA and LMWH was more frequent in patients with triple aPL positivity compared to single/double positivity (82.2% vs. 59.7%, respectively, $p = 0.001$). Moreover, combination therapy was used more frequently in patients satisfying the criteria for primary APS compared to aPL carriers (53.6% vs. 33.8%, $p = 0.005$). In multivariate analysis patients with complicated pregnancies were more frequently treated with combination therapy, LDA+LMWH ($p = 0.005$, OR 2.200, CI 95% 1.273–3.800); however, it did not relate with low preconception C3/C4 levels.

Lastly, we found in patients with triple aPL positivity (with and without APS) and complement consumption that the administration of HCQ on top of combination therapy during pregnancy was significantly related with a better gestational outcome compared to patients that had received only LDA+LMWH (70% vs. 23% did not present any APO, $p = 0.018$). This observation could not be confirmed in patients with single or double aPL positivity.

4. Discussion

This multicenter study allowed us to identify preconception decreased C3 and C4 levels as a predictive marker for the occurrence of APO in aPL-positive patients with or without clinical manifestations. In a large sample of 260 pregnancies, a decrease in preconception levels of C3/C4 levels were found in 36% of the patients. Overall, women with APO showed significant lower preconception complement levels than those with successful pregnancies, without any difference between APS and aPL carriers. As shown in univariate analysis, low preconception complement levels, mainly C3, resulted as significant risk factor for prematurity and pregnancy loss. This finding is in agreement with previous studies showing an association between low C3/C4 levels and APO [14,16,19]. Partially consistent data were raised by Deguchi and coworkers, who observed that only hypertensive pregnancy complication of APS but not fetal loss are related to decreased C3/C4 levels [14]. Other authors described lower complement levels in APS pregnant women compared to the obstetrical general population but without any relationship with pregnancy loss [13].

Unfortunately, findings emerging in different studies are not always easily comparable: complement determinations were performed in different weeks of gestation and it is well known that pregnancy itself exerts an important influence on the complement components synthesis [20–23]. Heterogeneity refers even to clinical criteria for study inclusion, with some studies enrolling exclusively women with primary APS and others also women with systemic autoimmune rheumatic conditions. To note, in our study patients with concomitant autoimmune diseases, especially systemic lupus erythematosus, were excluded to avoid bias. ANA positivity was found in 27% of cases, but none of the patients had any additional sign or symptom of SLE or other systemic autoimmune diseases. Autoimmune thyroid disease was found in 9.2%, partially accounting for the high ANA positivity rate.

If animal models have clearly shown that activation of complement is required to produce aPL-mediated pregnancy loss and inflammation and complement deposition at trophoblast and placental level was described [10], histopathological data from human disease are not consistent. In fact, human placenta analysis does not unanimously show complement deposition, and inflammation (chorioamnionitisis or villitis) does not seem always associated with aPL-mediated pregnancy loss [24,25].

This work also addressed the differential prognostic role of complement levels in patients stratified upon the aPL profile (triple versus single/double aPL positivity). The profile of triple aPL positivity is well known to identify patients at high risk for pregnancy loss [26]. Consequently, in this setting the combination therapy during pregnancy is strongly supported not only in patients with obstetrical APS only (without previous thrombosis) but also in aPL carriers, at least when multiple risk factors are identified [11,27,28]. In our study, triple aPL positivity was recorded in 23.8% of the whole cohort, most of the triple aPL-positive patients displayed low C3/C4 levels (77%). Despite the bias related to a better treatment approach and despite the relatively low number of triple aPL-positive pregnancies, low preconception levels of C3 and/or C4 significantly relate to pregnancy loss (p = 0.05). In the group of patients with single/double positivity, the pregnancy outcome was not related to the complement levels before pregnancy.

We also could confirm, in multivariate analysis, the association between APO and triple aPL positivity. Such association held significance even if in most pregnancies (81%) combination therapy (LDA and LMWH) was instituted. This finding suggests that pregnancies in patients with triple aPL positivity, independently from maternal diagnosis and from conventional treatment, seems to be more often characterized by complications. Recently, women with high-risk aPL profiles were found to have a probability of pregnancy morbidity as high as 52% despite conventional treatment (EUREKA). Not surprisingly, in this particular high-risk subgroup, the addition of immunomodulatory therapy has been suggested in literature, ranging from HCQ [29,30] as well as low-dose corticosteroids or intravenous immunoglobulins [31,32]. In our cohort, the therapeutic choices were formulated by the attending physicians, based on the clinical and laboratory profile as well as the pre-

vious obstetrical history of each patient. In particular, previous pregnancy failures despite combination therapy and the presence of the so-called "non criteria manifestations", which have been associated with possible poor gestational outcome [28], can support adding HCQ on top of conventional therapy. Of note, we observed that in triple aPL-positive patients with complement consumption, the addition of HCQ to the combination therapy is linked to a significantly reduced rate of APO. This positive effect on pregnancy complications was not observed in patients with normal complement levels. Positive effects of HCQ during pregnancy in APS patients were already described by other authors and suggested by EULAR recommendations that propose this additional treatment option [29,33].

We reported a low rate of maternal complications during pregnancy and/or puerperium. In particular, we reported three mothers with deep vein thrombosis. One patient with vascular APS suffered a deep vein thrombosis during the second trimester, while she was on LMWH at therapeutic dosage. Two women, one vascular and one obstetric APS, experienced venous thrombosis during puerperium in accordance with the well-known risk of postpartum thrombosis in the general obstetric population. In both cases, the patients were in prophylactic therapy with LMWH.

We also observed 14 pregnancies (5%) complicated by PE/HELLP syndrome, 6 of them were patients with a triple positivity for aPL (4 APS).

In the group of pregnancies with maternal complications, we did not find any statistical correlation with low preconception C3/C4 levels in contrast with what has been reported by other authors [34].

This study has several limitations: the retrospective design, which could have led to possible completeness and registration bias; the lack of a centralized laboratory, which could be considered not so relevant since only routine assays were included in the study; the multicenter nature, a possible source of heterogeneity.

However, the study also has several strengths: the inclusion of a large number of pregnancies in patients with aPL/APS, regularly followed throughout their gestational period; the useful application of simple and cheap laboratory tests, such as C3 and C4 levels that are routinely and widely performed; the inclusion of patients from twelve different centers, which testifies to the solid nature of the obtained results.

In conclusion, this study shows that low levels of C3 and C4 in aPL/APS patients are linked to a worse pregnancy outcome, even in patients with triple antibody positivity, which already carries a bad prognosis. Therefore, C3 and C4 complement assay, which are inexpensive and routinely available, could provide a valid tool to better stratify the risk of pregnancy morbidity in women carrying aPL. Given the high rate of unresponsiveness to treatment we still observe among aPL-positive women embarking on a pregnancy, it would be valuable to early identify women that could possibly benefit from a closer monitoring and a more aggressive therapeutic approach, such as the addition of HCQ to conventional treatment.

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Allegato 8

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Original article

Are remission and low disease activity state ideal targets for pregnancy planning in systemic lupus erythematosus? A multicentre study

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Abstract

Objectives. To determine whether disease remission or low disease activity state at the beginning of pregnancy in SLE patients is associated with better pregnancy outcome.

Methods. Pregnancies in SLE patients prospectively monitored by pregnancy clinics at four rheumatology centres were enrolled. Patient demographics and clinical information were collected at baseline (pregnancy visit before 8 weeks of gestation) including whether patients were in remission according to the Definition of Remission in SLE (DORIS) criteria and and/or Lupus Low Disease Activity State (LLDAS). Univariate and multivariate analysis were performed to determine predictors of disease flare and adverse pregnancy outcomes (APOs) including preeclampsia, preterm delivery, small for gestational age infant, intrauterine growth restriction and intrauterine fetal death.

Results. A total of 347 pregnancies were observed in 281 SLE patients. Excluding early pregnancy losses, 212 pregnancies (69.7%) occurred in patients who were in remission at baseline, 33 (10.9%) in patients in LLDAS, and the remainder in active patients. Seventy-three flares (24%) were observed during pregnancy or puerperium, and 105 (34.5%) APOs occurred. Multivariate analysis revealed that patients in disease remission or taking HCQ were less likely to have disease flare, while a history of LN increased the risk. The risk of APOs was increased in patients with shorter disease duration, while being on HCQ resulted a protective variable. An almost significant association between complete remission and a decreased risk of APOs was observed.

Conclusions. Prenatal planning with a firm treat-to-target goal of disease remission is an important strategy to reduce the risk of disease flares and severe obstetric complications in SLE pregnancies.

Key words: pregnancies, SLE, remission, low disease activity state, disease flare

CLINICAL SCIENCE

Rheumatology key messages

- Disease remission should be regarded as a major aim to secure a better pregnancy outcome.
- Residual disease activity at conception could represent a risk factor for flares during pregnancy.
- Patients who remain in low grade of disease activity should be monitored closely.

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Introduction

SLE is a chronic autoimmune disease with a wide range of clinical manifestations and a relapsing–remitting course. An international panel of experts recently developed a framework for defining SLE remission (Definition of Remission in SLE, DORIS) [1], which identifies patients in complete remission with negative SLE serology or clinical remission, while they remain on or off treatment. This is distinct from patients who are in low disease activity, which can be assessed by a validated index called Lupus Low Disease Activity State (LLDAS) [2]. Disease activity is associated with increased rate of organ damage progression [3], while sustained remission and LLDAS are associated with reduced damage accrual [4–9], better quality of life [10, 11] and reduced hospitalizations [12]. Remission or LLDAS are therefore currently considered the ideal treatment target and possible starting point for treatment reduction [13].

To date, there are few cohort studies investigating whether disease activity can influence pregnancy outcome in SLE [14–17] but none applied specific disease activity states as remission or LLDAS.

It is widely recognized that active SLE prior to or at conception is associated with a higher risk of maternal and fetal morbidity and mortality [18], including flares during pregnancy and puerperium [19, 20], pre-eclampsia [21, 22], intrauterine growth restriction [23], pregnancy loss [24, 25] and preterm delivery [22, 24–29]. Prenatal counselling to assess the presence of risk factors associated with poor pregnancy outcomes including disease activity is therefore recommended by the 2016 EULAR SLE guidelines for the management of women's reproductive health [30] and by the 2020 ACR Guidelines for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases [31]. Counselling is therefore crucial for determining the safety and timing of pregnancy and for implementing appropriate preventative strategies to avoid active lupus or flaring prior to conception.

However, the precise level of disease activity that should be targeted prior to pregnancy remains unclear. Given the high stakes associated with active disease and disease flare during pregnancy, a more aggressive treat-to-target strategy towards remission may be preferable. In the PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and SLE) study of 385 SLE patients with inactive or stable mild/moderate disease during the first trimester [14], about a fifth of these patients still experienced an adverse pregnancy outcome including fetal or neonatal death (5%). These patients also had mild flares during pregnancy that were predicted by younger age and clinical and serological activity at baseline [15]. In their study of 96 women who were pregnant with low disease activity, Kroese *et al.* similarly found that pregnancy complications were still present (50% developed at least one pregnancy complication) [32].

Despite this, SLE patients are still advised to consider pregnancy when they have 'minimal' or 'stable' disease for at least 4–6 months [14, 21, 33–35], even though definitions of 'minimal' or 'stable' disease activity vary from study to study. Further clarification on which endpoint clinicians should target is therefore necessary. This study aims to evaluate the effect of remission and LLDAS on pregnancy outcome in SLE patients.

Methods

Study population

This is a retrospective study involving pregnancies in SLE patients prospectively monitored by the Pregnancy Clinic at four rheumatology centres (Universities of Brescia, Dusseldorf, Padova and Pisa) between 1995 and 2018. Our cohort includes adult patients with SLE satisfying the 1997 ACR classification criteria [36]. As soon as a pregnancy was confirmed, each patient was monitored on a monthly basis by both a rheumatologist and an obstetrician. The first visit before 8 weeks of gestation was considered the study baseline visit and the follow-up period ended after the last visit during the postpartum period. Clinical and demographic data from the previous 6 months were retrieved from clinical charts. Pregnancy losses at or before 12 weeks of gestation were analysed separately.

This study was approved by the ethics committee 'Comitato Etico Area Vasta Nord Ovest' and informed consent was obtained by all patients.

Definitions and outcome measures

Disease activity was assessed according to Safety of Estrogens in Lupus Erythematosus: National Assessment-SLEDAI (SELENA-SLEDAI) as well as physician global assessment (PGA) on a scale of 0–3. Remission was defined according to the DORIS definition [1] and patients were subsequently grouped into the following four categories: clinical remission on treatment; clinical remission off treatment; complete remission on treatment; and complete remission off treatment. LLDAS was defined on the basis of the Asian Pacific Lupus Consortium definition [2]. We considered remission to be stable if it was confirmed both at last visit before pregnancy (performed within 6 months) and at baseline.

The outcomes of the study were disease flare and adverse pregnancy outcomes (APOs).

Disease flares have been defined according to the SELENA-SLEDAI flare index as mild/moderate flares or severe flares, and APOs defined as at least one of the following events: intrauterine fetal death after 12 weeks of gestation; preterm delivery before 37 weeks' gestation; preeclampsia; intrauterine growth restriction; and small for gestational age infant. Small for gestational age was defined as birthweight $<$10th percentile. Preeclampsia was defined as new-onset hypertension (blood pressure $\geq$140 mmHg systolic and $\geq$90 mmHg diastolic) after 20 weeks of gestation and proteinuria ($>$300 mg/24 h), as these criteria are included in all the international guidelines used during the study recruitment period [37, 38]. Intrauterine growth restriction was defined

as US biometric fetal measurements <10th centile associated with anomalies of Doppler umbilical or uterine velocimetry; these criteria are in line with the consensus-based definitions recently agreed upon by an expert consensus using the Delphi procedure [39]. Early pregnancy losses were defined as the spontaneous demise of the pregnancy at or before 12 weeks of gestation.

Statistical analysis

Continuous variables were described as median and 25–75 interquartile range (IQR) or as mean (S.D.) as appropriate. Categorical variables are reported as proportions. In the univariate analysis, we assessed for predictors of disease flare and APOs using *t*-tests and the non-parametric Wilcoxon tests. Cross-tabulated data were analysed using Chi-squared test. Multivariate analyses, including variables with a $P < 0.05$ in the univariate analysis and clinically relevant variables, were performed using the logistic regression model. *P*-values of <0.05 were considered to be statistically significant and odds ratio (OR) with 95% CI were reported. The following variables were included in the analysis: age; disease duration; type of organ involvement (cumulative); comorbidities (hypertension, obesity, APS, chronic renal failure and hypothyroidism); disease activity during pregnancy (SLEDAI, PGA); subtypes of DORIS remission; LLDAS; antibody profile detected at local labs; flare during pregnancy or puerperium; treatment during pregnancy; pregnancy outcome; and obstetric complications. Listwise deletion was the method used in handling missing data.

In all models robust standard errors were used to control for clustered data. All analysis was performed using STATA-13 Statistical Software (StataCorp LLC, College Station, TX).

Results

Patients

A total of 347 pregnancies in 281 patients were considered.

All patients fulfilled at least four of the 1997 ACR classification criteria; namely, in 103 (46.8%), 58 (26.4%), 43 (19.5%) and 16 (7.3%) pregnancies, four, five, six or seven were satisfied, respectively. These data were not available for the remaining 127 pregnancies because of missing data.

The mean () maternal age at conception was 31.9 years (S.D. 4.5) and the median duration of the disease at the time of pregnancy was 8 years (IQR 4–13). In seven cases (2.0%), pregnancy was the result of medically assisted reproduction and in 151 cases (43.5%) it was the first pregnancy. The most prevalent organ involvement was musculoskeletal (62.5%), followed by cutaneous (53.6%), renal (38.0%) and haematological (31.7%). Almost in all cases (99.4%) patients were ANA positive, while anti-dsDNA antibodies were positive in 57.6% pregnancies, ENA in 51.6% and aPL in 32.3%. Table 1 reports the prevalence of autoantibodies, clinical characteristics and comorbidities. A diagnosis of APS was also notably present in 43 (12.4%) pregnancies. Table 1 also reports medications at baseline.

Out of 347 pregnancies, 43 early pregnancy losses occurred (12.4%) in 40 patients (supplementary Table S1, available at *Rheumatology* online). At the last visit prior to pregnancy or at first visit during pregnancy, disease was active in 7 cases (16.3%), while LLDAS, LLDAS without remission and remission were observed in 36 (83.7%), 1 (2.3%) and 35 cases (81.4%), respectively.

At univariate analysis, first trimester pregnancy loss was not associated with active disease at the beginning of pregnancy (10.6% in cases of active disease *vs* 12.81% in cases of inactive disease, $P = 0.61$).

The above pregnancies, spontaneously lost before 12 weeks of gestation, were excluded from the following analyses.

Table 1 Baseline characteristics of the cohort ($N = 347$)

Age, years [mean (S.D.)]	**31.9 (4.5)**
Median disease duration, years (IQR)	8 (4–13)
First pregnancy [*n* (%)]	134 (44.1)
Type of autoantibodies (%)	
ANA	99.4
Anti-dsDNA	57.6
Anti-ENA	51.6
Anti-Ro and/or anti-La	39.8
aPL	32.3
aCL	17.6
LA	17.6
Anti-β2GPI	16.4
Triple aPL positivity	7.0
Manifestations of the disease (at any time during disease course) (%)	
Articular	62.5
Cutaneous	53.6
Renal	38.0
Haematological	31.7
Serositis	13.0
Comorbidities (%)	
Hypertension	13.0
APS	12.4
Hypothyroidism	7.8
Obesity (BMI ≥30 kg/m^2)	6.1
Chronic renal failure	0.3
Treatment at baseline	
Glucocorticoids (%)	53.3
Median dose prednisone equivalent	5 mg/day
HCQ (%)	55.0
AZA (%)	23.3
Ciclosporin (%)	5.8
IVIG (%)	1.7
Low-dose aspirin (%)	53.6
Low molecular weight heparin (%)	21.6
Combination therapy with glucocorticoids and AZA (%)	19.9
Combination therapy with glucocorticoids and ciclosporin (%)	4.3

Note: multiple drugs were associated in some patients. IQR: interquartile range; anti-β2GPI: anti-β2-GPI antibodies.

Disease activity prior to and at start of pregnancy

At the last visit prior to pregnancy (performed within 6 months) disease was active in 49 cases (16.1%), whereas LLDAS and LLDAS without remission were observed in 206 (67.8%) and 30 cases (9.9%), respectively. Disease activity could not be evaluated in 19 patients due to lack of clinical data. In the 49 cases of active disease median SELENA-SLEDAI score was 6 (IQR 4–6) and we recorded 23 cases of active renal involvement with proteinuria and/or haematuria, and also cases of active haematological, articular and mucocutaneous involvement (6, 3 and 1 cases respectively).

At the first visit during pregnancy, the median SLEDAI was 2 (IQR 0–4) and median PGA was 0 (IQR 0–0.2); in 33 cases (10.9%), SLEDAI was >4. The disease was active in 59 cases (19%) while most cases showed LLDAS ($n = 245$, 81%). Notably, 33 (10.9%) cases showed LLDAS but not remission. In cases of active disease median SELENA-SLEDAI score was 5 (IQR 4–6). We recorded 23 cases of active renal involvement with proteinuria and/or haematuria, and also cases of active articular, mucocutaneous and haematological involvement (10, 8 and 4 cases, respectively).

Fig. 1 reports the categories of remission. Remission was also stable in most cases (89.1%).

Disease flares

In 73 cases (24%), the patient flared during pregnancy or puerperium. The incidence of flare was 6.25, 10.86, 6.25 and 2.63% during first, second, third trimester and puerperium, respectively. Five patients had severe flares and 68 mild-moderate flares. A detailed description of the disease flares was available only in 33 (45.2%) patients. Among these, patients developed renal flare in 10 cases, hematological in 9, articular in 6, cutaneous in 3 and neurological in 1. One patient presented in catastrophic APS with middle cerebral artery thrombosis. Two patients developed multiple complications, one with cutaneous and articular involvement and the other with cutaneous and renal involvement.

Table 2 reports the clinical characteristics of patients who flared compared with those who did not flare. Patients who flared were younger at pregnancy [29.9 (4.3) *vs* 32.2 (4.6) years, $P < 0.01$], had a shorter disease duration [7.5 (4.6) *vs* 9.6 (6.2), $P = 0.02$] and were more likely to have a history of LN (52.1 *vs* 34.2%, $P < 0.01$). At baseline, they had lower C3 [84.9 (25.4) *vs* 93.6 (22.5), $P = 0.01$] and C4 values [13.3 (7.1) *vs* 16.1 (8.1), $P = 0.01$], higher disease activity scores [SLEDAI 3.7 (2.4) *vs* 2.1 (1.8), $P < 0.01$] and higher PGA scores [0.5 (0.7) *vs* 0.2 (0.4), $P < 0.01$].

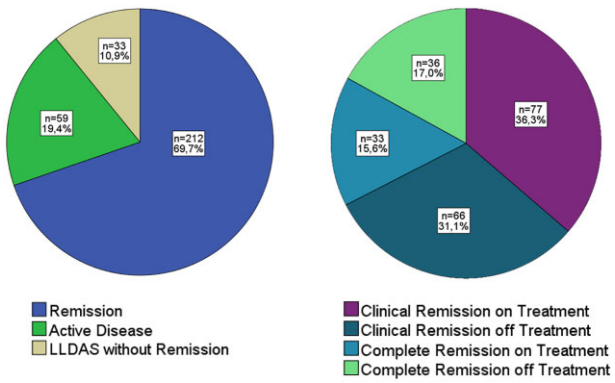
Patients who did not flare were more likely to be in LLDAS and remission at first visit during pregnancy (89.2% in LLDAS among patients who did not flare *vs* 52.1% among patients who flared, $P < 0.01$; 80.8% in remission among patients who did not flare *vs* 38.3% among patients who flared, $P < 0.01$). Regarding treatment at pregnancy outset, the percentage of patients on glucocorticoids was significantly higher among patients who flared (67.1 *vs* 52.8%, $P = 0.02$); a similar situation was observed with AZA (38.4 *vs* 21.2%, $P < 0.01$). Conversely, patients who did not flare were more likely to be treated with HCQ (65.0 *vs* 41.1%, $P < 0.01$).

Pregnancy outcomes

Nine pregnancies (3%) ended with intrauterine death of fetuses without structural or chromosomal anomalies, and the remaining 295 (97%) ended with a live birth. The median duration of the pregnancies ending with a live-birth was 38 weeks (IQR 37–39) and birthweight median value was 3010 g (IQR 2610–3290). Table 3 details obstetric complications that were observed in 105 pregnancies (34.5%), including 28 cases (9.2%) of preeclampsia, 71 cases (24%) of preterm delivery and 36 cases (12.2%) of small for gestational age.

Table 4 reports the clinical characteristics of patients with APOs compared with patients without APOs. Shorter disease duration, hypertension, anti-dsDNA, LA and triple aPL positivity were significantly associated with APOs [7.9 (5.1) *vs* 9.7 (6.3) years, $P = 0.02$, 22.0 *vs*

Fig. 1 Disease activity at the beginning of pregnancy and types of remission



LLDAS: Lupus Low Disease Activity State.

Table 2 Univariable analysis of baseline clinical characteristics between patients who flared and patients who did not flare

	Patients who flared during pregnancy, $N = 73$	Patients who did not flare during pregnancy, $N = 231$	*P*-value
Age, years [mean (S.D.)]	29.9 (4.3)	32.2 (4.6)	**<0.01**
Disease duration, years [mean (S.D.)]	7.5 (4.6)	9.6 (6.2)	**0.02**
History of LN (%)	52.1	34.2	**<0.01**
Hypertension (%)	20.5	11.7	0.6
Obesity (%)	9.6	5.2	0.41
Chronic renal failure	0	0.4	0.62
APS (%)	13.7	11.7	0.62
aPL (%)	30.1	32.9	0.66
LA (%)	17.8	17.7	0.91
Triple aPL positivity (%)	2.7	8.6	0.08
Anti-dsDNA (%)	65.8	53.2	0.06
Anti-Ro and/or anti-La (%)	35.6	43.3	0.24
C3 [mean (S.D.)]	84.9 (25.4)	93.6 (22.5)	**0.01**
C4 [mean (S.D.)]	13.3 (7.1)	16 (8.1)	**0.01**
SLEDAI [mean (S.D.)]	3.7 (2.4)	2.1 (1.8)	**<0.01**
PGA [mean (S.D.)]	0.5 (0.7)	0.2 (0.4)	**<0.01**
LLDAS without remission (%)	16.4	9.1	0.07
LLDAS (%)	52.1	89.2	**<0.01**
Clinical remission (on–off treatment) (%)	31.5	52.8	**<0.01**
Complete remission (on–off treatment) (%)	6.8	28.0	**<0.01**
Glucocorticoids (%)	67.1	52.8	**0.02**
HCQ (%)	41.1	65.0	**<0.01**
AZA (%)	38.4	21.2	**<0.01**
Ciclosporin (%)	2.7	5.2	0.6
Smoking during pregnancy %	1.4	0.4	0.37

PGA: physician global assessment; LLDAS: Lupus Low Disease Activity State. Bold P values were <0.05 and were considered to be statistically significant.

Table 3 Obstetric complications

IUFD (%)	3
Obstetric complications in pregnancies yielding a live birth (%)	34.5
Preterm delivery <37 gw (%)	24
Median gestational age at preterm delivery (weeks) (IQR)	34 (31–36)
Severe preterm <32 gw (%)	8.8
Preterm PROM <37 gw (%)	5.6
IUGR (%)	2.6
Preeclampsia (%)	9.2
Gestational diabetes (%)	1.9
Birthweight <2500 g (%)	18.6
Birthweight <1500 g (%)	5.7
SGA infant (%)	12.2

Note: More than one complication occurred in 45 pregnancies. IUFD: intrauterine fetal death; gw: gestational week; IQR: interquartile range; PROM: preterm prelabour rupture of membranes; IUGR: intrauterine growth restriction; SGA: small for gestational age.

9.5%, $P = 0.05$, 64.7 *vs* 51.8%, $P = 0.03$, 23.8 *vs* 14.6%, $P = 0.04$, 13.3 *vs* 4.0%, $P < 0.01$, respectively]. Disease activity score was significantly higher in patients with APOs [(2.9 (2.2) *vs* 2.2 (2.0), $P < 0.01$] and a lower proportion of them were in LLDAS, remission (any) and complete remission (69.5 *vs* 86.0%, $P = 0.001$, 59.0 *vs* 76.3%, $P < 0.01$ and 13.3 *vs* 27.6%, $P < 0.01$, respectively). As far as treatment is concerned, patients with APOs were less likely to be on HCQ (50.5 *vs* 63.8%, $P = 0.02$) and more likely to be on AZA (33.3 *vs* 21.1%, $P = 0.02$).

APOs were observed more frequently in patients who experienced a disease flare during pregnancy and, in

TABLE 4 Univariable analysis of baseline clinical characteristics of patients with APOs compared with patients without APOs

	APO, $N = 105$	No APO, $N = 199$	P-value
Age, years [mean (S.D.)]	31.2 (4.4)	31.8 (4.7)	0.19
Disease duration, years [mean (S.D.)]	7.9 (5.1)	9.7 (6.3)	**0.02**
History of LN (%)	38.1	38.7	0.9
Pre-pregnancy hypertension (%)	22.0	9.5	**0.05**
Obesity (%)	7.6	5.5	0.8
Chronic renal failure	1.0	0	0.15
APS (%)	17.1	9.5	0.07
aPL (%)	39.0	28.6	0.06
LA (%)	23.8	14.6	**0.04**
aCL (%)	27.6	21.6	0.26
Anti-β2GPI (%)	18.1	13.1	0.24
Triple aPL positivity (%)	13.3	4.0	**<0.01**
anti-dsDNA (%)	64.7	51.8	**0.03**
anti-Ro and/or anti-LA (%)	39.0	42.7	0.53
C3 [mean (S.D.)]	90.3 (25.0)	92.1 (22.8)	0.7
C4 [mean (S.D.)]	14.7 (7.4)	15.6 (8.2)	0.44
SLEDAI [mean (S.D.)]	2.9 (2.2)	2.2 (2.0)	**<0.01**
PGA [mean (S.D.)]	0.3 (0.5)	0.2 (0.4)	0.2
LLDAS without remission (%)	12.4	10.1	0.53
LLDAS (%)	69.5	86.0	**<0.01**
Remission (any %)	59.0	76.3	**<0.01**
Clinical remission (%)	45.7	48.7	0.6
Complete remission (%)	13.3	27.6	**<0.01**
Glucocorticoids daily dose [mean (S.D.)]	6.8 (5.2)	5.7 (3.2)	0.52
HCQ (yes/no) (%)	50.5	63.8	**0.02**
AZA (yes/no) (%)	33.3	21.1	**0.02**
Ciclosporin (yes/no) (%)	4.8	4.5	0.6
Low dose aspirin (yes/no) (%)	62.8	55.3	0.20
Low molecular weight heparin (yes/no) (%)	30.4	21.1	0.07

APO: adverse pregnancy outcome; LLDAS: Lupus Low Disease Activity State. Bold P values were <0.05 and were considered to be statistically significant.

particular, renal flares (49.3 *vs* 29.9%, $P < 0.01$ and 75.0 *vs* 30.6%, $P < 0.01$, respectively).

Predictors of disease flare and APOs

Table 5 shows the results of the multivariate analysis. Renal involvement at baseline was associated with an increased risk of disease flare (OR 2.36, 95% CI 1.07, 5.20, $P = 0.032$) while remission (both complete and clinical) and ongoing treatment with HCQ were associated with a decreased risk of flare (OR 0.29 95% CI 0.10, 0.82, $P = 0.02$ and OR 0.20 95% CI 0.09, 0.42, $P < 0.01$, respectively).

The risk of APOs was increased in patients with shorter disease duration (OR 0.94 95% CI 0.90, 0.99, $P = 0.04$) while treatment with HCQ resulted protective against APOs (OR 0.56, 95% CI 0.32, 0.96, $P = 0.04$). Of note, among disease states, only complete remission tended to be associated with a lower risk of APOs (OR 0.42, 95% CI 0.17, 1.00, $P = 0.05$).

The remaining baseline variables that were significantly associated with disease flares or APOs in the univariable analysis lost their significance at multivariable analysis.

Discussion

Pregnancy in SLE patients is considered a high-risk condition with increased frequency of disease flares and obstetric complications, especially in the case of high disease activity [40]. Definitions for disease remission and LLDAS have been recently proposed and validated as targets to be achieved in SLE management as they are associated with better disease outcome [4–12]. Using real-world evidence from a multicentric cohort of 347 pregnancies in 281 SLE patients, the aim of this study was to determine whether disease remission and LLDAS at the start of pregnancy are associated with better pregnancy outcomes with lower risk of flares and severe obstetric complications.

We decided to analyse first trimester pregnancy loss separately from other obstetric complications on the basis of the following considerations: first trimester pregnancy loss usually does not affect maternal mortality

Table 5 Multivariate analysis for predictors of disease flares and adverse pregnancy outcomes

	OR	*P*-value	CI
Flare			
LLDAS at study entry	0.54	0.24	0.19, 1.53
Age at study entry	0.97	0.59	0.89, 1.06
Disease duration	0.96	0.24	0.90, 1.02
History of LN	2.36	**0.032**	1.07, 5.20
Anti-dsDNA	1.06	0.88	0.43, 2.61
C3	0.98	0.22	0.96, 1.00
C4	1.00	0.85	0.95, 1.05
HCQ	0.20	**<0.01**	0.09, 0.42
Glucocorticoids	1.68	0.16	0.80, 3.54
AZA	0.97	0.94	0.43, 2.12
SLEDAI at study entry	1.19	0.16	0.92, 1.55
PGA at study entry	0.80	0.66	0.30, 2.11
Remission (any) at study entry	0.29	**0.02**	0.10, 0.82
Clinical remission	0.27	**0.01**	0.09, 0.79
Complete remission	0.35	**0.02**	0.14, 0.86
APO			
LLDAS at study entry	0.53	0.45	0.10, 2.75
LLDAS without remission at study entry	3.43	0.13	0.69, 16.97
Disease duration	0.94	**0.04**	0.90, 0.99
Hypertension	1.87	0.09	0.89, 3.82
Anti-dsDNA	0.87	0.73	0.40, 1.89
SLEDAI at study entry	1.03	0.71	0.84, 1.26
LA	2.16	0.07	0.93, 5.00
Triple aPL positivity	1.24	0.74	0.32, 4.79
HCQ	0.56	**0.04**	0.32, 0.96
AZA	1.39	0.30	0.74, 2.60
Remission (any)	1.25	0.72	0.36, 4.32
Complete remission	0.42	0.05	0.17 to1.00

OR: odds ratio; LLDAS: Lupus Low Disease Activity State; PGA: physician global assessment; APO: adverse pregnancy outcome. Bold P values were <0.05 and were considered to be statistically significant.

and morbidity and has no long-term consequences on the population health, such as neurodevelopmental sequelae, at variance with late APOs [41, 42]. As for patients with aPL, it has been suggested that women with recurrent early pregnancy loss should not be grouped with those with late loss or early delivery due to placental mediated complications [43]. Additionally, ascertainment of early pregnancy losses is likely to be far from complete, especially when the data are collected in a dedicated obstetric/rheumatologic clinic where patients may attend their first medical visit only after the diagnosis of pregnancy and of embryo viability has been established at a peripheral level. Finally, as genetic factors represent common causes of pregnancy loss in the first trimester and they are not routinely investigated [44], it is often impossible to establish the cause of each early pregnancy loss. Taking into account these limitations and possible biases, we recorded a 12.4% rate of first trimester pregnancy losses, which is similar to data from the general population [45, 46]; moreover, no association between early pregnancy loss and pregestational disease activity was found.

Excluding early pregnancy losses, the majority of patients (81%) were in LLDAS at the start of pregnancy and of these patients, 86.5% also fulfilled the DORIS remission criteria. Despite this, disease flares were reported in 24% of pregnancies, which is similar to the frequency observed in the Kroese *et al.* study as well as in the PROMISSE study [15, 32]. Nevertheless, this study demonstrated that the frequency of APOs was 34.5%, which is higher than the data reported in PROMISSE [14]. The difference might be accounted for by variables in patient population and the definition of APOs. Unlike the PROMISSE study, this study included unselected patients with high disease activity, on medium or high dosages of glucocorticoids, with relevant comorbidities such as hypertension. One of the strengths of this study is that its results may be considered more generalized due to wider inclusion criteria. Kroese *et al.*'s study [32], like this study, did not apply exclusion criteria concerning disease activity, comorbidity or medication use with APOs occurring in 42.7% of their patients.

At univariate analysis, pregnancy outcome was significantly better in patients with LLDAS and/or remission compared with patients with active disease at the start of pregnancy. At the multivariate analysis phase, however, only remission seems to be the best predictor of a good outcome; remission was independently associated with fewer disease flares ($P = 0.02$), with no significant differences between clinical and complete remission, while only complete remission tended to be protective against APOs ($P = 0.05$).

This result is of pivotal importance during pregnancy planning since it suggests that disease remission should be regarded as a major aim to secure a better outcome. On the other hand, these data also suggest that residual disease activity at conception could represent a risk factor for flares during pregnancy.

Treatment with HCQ was notably another protective variable independently associated with better outcomes in term of disease flares ($P < 0.01$) and APOs ($P = 0.04$). These results are in line with previous reports showing the benefit of HCQ for pregnancy complications [47–49] and disease activity [50–52], therefore promoting the maintenance of this drug during pregnancy.

Moreover, we also recorded a higher percentage of patients on glucocorticoids and AZA among patients who flared and a higher percentage of patients taking AZA among those with APO. Such results might be accounted for by a more severe disease phenotype.

Our data also confirmed the role of LN history as a predictor of disease flare in agreement with the results of previous studies [21, 53], but did not confirm its association with obstetric complications [35]. Moreover, in the multivariate analysis, hypertension lost the association with pregnancy complications, in contrast to that found in pregnancies from LN cohorts [28, 54]. The lower prevalence of hypertension in our cohort could be

a possible explanation. As expected, LA and triple aPL positivity was associated with APOs, although the statistical significance was almost lost at multivariate analysis; other serological parameters did not demonstrate a similar impact.

Finally, patients who experienced flares during their pregnancies had a higher risk of APOs: this observation may be relevant in pre-pregnancy counselling, when SLE patients can be made aware that the wellbeing of the fetus is significantly related to the wellbeing of the mother.

Our study does, however, possess several limitations. Firstly, it is a retrospective study, even though our data derived from a real-life practice of four European referral centres for pregnancy in SLE and were carefully collected. Secondly, we acknowledge that disease activity was assessed using SLEDAI rather than SLEPDAI (SLEDAI adjusted for pregnancy) [55], as it was used for the definitions of LLDAS and remission. Similarly, we chose the DORIS definitions for remission instead of other definitions because they included a PGA as we felt it important to include the PGA in our analysis due to the necessity of overcoming limits intrinsic to the SLEDAI during pregnancy by providing an overall judgment by the treating physician.

On the other hand, one of the major strengths of this study is that it reflects the real-world setting in SLE referral centres, as patients with high disease activity or comorbidities were not excluded. This makes the results of the study generalizable to day-to-day practice. This is also the first study analysing the impact on pregnancy outcomes of different categories of disease state as defined by LLDAS and remission criteria.

In conclusion, this study reinforces the importance of prenatal planning and targeting definite disease remission to ensure a more favourable pregnancy outcome. Patients who are unable to achieve remission and remain in low grade of disease activity are still at risk of disease flare and obstetrical complications, and should therefore be monitored closely.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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Allegato 9

LUPUS SCIENCE & MEDICINE™

Impact of low-dose acetylsalicylic acid on pregnancy outcome in systemic lupus erythematosus: results from a multicentre study

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ABSTRACT

Objective It is still a matter of debate whether low-dose acetylsalicylic acid (LDASA) should be prescribed to all patients with SLE during pregnancy. This study aimed at investigating the impact of LDASA on pregnancy outcomes in patients with SLE without history of renal involvement and without antiphospholipid antibodies (aPL).

Methods This is a retrospective analysis of prospectively monitored pregnancies at seven rheumatology centres. Previous/current renal involvement and aPL positivity were the exclusion criteria. Adverse pregnancy outcome (APO) is the composite outcome of the study and included proteinuric pre-eclampsia, preterm delivery <37 weeks, small-for-gestational age infant, low birth weight <2500 g, intrauterine growth restriction and intrauterine fetal death after 12 weeks of gestation of a morphologically normal fetus.

Results 216 pregnancies in 187 patients were included; 82 pregnancies (38.0%) were exposed to LDASA treatment. No differences in terms of age at conception, disease duration, clinical manifestations, comorbidities and disease flare during pregnancy were observed between patients taking LDASA and those who did not take LDASA during pregnancy. APO was observed in 65 cases (30.1%), including 13 cases (6.1%) of pre-eclampsia. The incidence of all complications was similar in the two groups. However, it is interesting to note that pre-eclampsia had lower frequency in patients taking LDASA versus those not taking LDASA (2.4% vs 8.3%, p=0.14).

Conclusions In pregnant patients with SLE without renal involvement and were aPL-negative, there is a low risk of severe obstetric complications, such as early pre-eclampsia. LDASA treatment does not provide a statistically significant advantage over these complications. However, a careful individual risk–benefit balance is warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The protective role of low-dose acetylsalicylic acid (LDASA) treatment against pre-eclampsia is well established in patients with SLE with previous renal involvement and/or antiphospholipid antibodies (aPL), but whether LDASA should be prescribed to all patients with SLE during pregnancy is still a matter of debate.

WHAT THIS STUDY ADDS

⇒ In our cohort, patients with SLE without renal involvement and were aPL-negative seem to have a low risk of severe obstetric complications such as early pre-eclampsia, and LDASA does not provide a significant advantage over these complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ In patients with SLE without renal involvement and were aPL-negative, LDASA does not seem to provide a significant protection against severe obstetric complications.

⇒ A careful individual risk–benefit balance is warranted.

INTRODUCTION

Pregnant patients with SLE is considered at risk of maternal and fetal complications resulting in high rates of preterm birth, pre-eclampsia and fetal loss compared with the general population, especially in the presence of antiphospholipid antibodies (aPL), active disease and renal involvement.[1 2]

The protective role of low-dose acetylsalicylic acid (LDASA) against pre-eclampsia is well established in non-autoimmune patients at high risk of this obstetric complication, as well as in patients with SLE with previous renal involvement and/or aPL.[3–5]

Indeed, LDASA is recommended by the 2017 European Alliance of Associations for Rheumatology recommendations for management of women's reproductive health[6] in patients with SLE at risk of pre-eclampsia, especially those with previous lupus nephritis or were aPL-positive. The 2020 American College of Rheumatology (ACR) Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases suggests treatment with LDASA in all pregnant women with SLE.[7] However, the committees acknowledge the lack of actual data. Also, the American College of Obstetricians and Gynecologists recommendations report autoimmune diseases among the high-risk factors, suggesting the use of LDASA.[8]

Although there are no studies on this target population, it has been postulated that LDASA could lower the risk of obstetric complications in SLE to an extent comparable with the risk reduction demonstrated in trials assessing LDASA treatment for other high-risk groups.[5 9]

This study aimed to test whether LDASA exposure during pregnancy in patients with SLE without history of renal involvement and without aPL is associated with better pregnancy outcomes, since published data on this topic are still scarce or absent.

METHODS

This is a retrospective study involving pregnancies in patients with SLE prospectively followed by the pregnancy clinic at seven rheumatology referral centres (university medical centres of Brescia, Düsseldorf, Ferrara, Milano, Padova, Pavia and Pisa) between 1995 and 2021. Our multicentre cohort included patients with SLE fulfilling the ACR 1997 classification criteria.[10]

Previous/current renal involvement as defined by the ACR criteria[11] and any positive result by either lupus anticoagulant, IgG/IgM anticardiolipin antibodies and IgG/IgM anti-beta-2-glycoprotein I in medium or high titre on two or more consecutive occasions at least 12 weeks apart were the exclusion criteria.

Clinical and serological data were retrieved from clinical charts. Disease activity was recorded at first evaluation (within 8 weeks of gestation) and monitored thereafter every month. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was used to categorise active disease (clinical SLEDAI >0) and disease flares have been defined according to the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI Flare Index.

Patients started LDASA at the first evaluation during pregnancy or at least within the first trimester; only pregnancies in which therapy was continued throughout the pregnancy were included. Twin pregnancies were excluded.

Adverse pregnancy outcome (APO) was the composite primary outcome of the study and included proteinuric pre-eclampsia,[12] preterm delivery before 37 weeks of gestation, small-for-gestational age infant, low birth weight less than 2500 g, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) after 12 weeks of gestation of a morphologically normal fetus. Preterm delivery was defined severe when it occurred before 32 weeks of gestation, and birth weight was defined very low if the newborn weighed less than 1500 g.

Informed consent was obtained from all patients and was registered on medical records.

Statistical analysis

The characteristics of the pregnancies, overall and by treatment, were described in terms of frequencies and percentages for categorical variables and median and IQR for continuous variables.

The data presented three nested levels of variations: pregnancy within a woman within a centre. The association of the composite outcome with the use of LDASA was assessed by a Bayesian mixed-effect logistic model[13] with woman as the random effect, with and without adjustment for potential confounders, including age at pregnancy, primiparity, hypertension, active disease at first visit and disease flares during pregnancy. The estimated OR and the corresponding 95% CI for the treatment effect were calculated. The variable centre was not included in the model because there was no evidence of heterogeneity in outcome among centres. The statistical software R V.4.1.1[14] with its package blmer was used for analyses.

RESULTS

The study included 216 pregnancies from 187 women (162, 21 and 4 with one, two and three pregnancies, respectively) from seven referral centres. Four patients were African, and the others Caucasian.

Baseline characteristics at conception

The characteristics of pregnancies are described in table 1.

The median age and disease duration at conception were 32 (IQR 30–36) years and 9 (IQR 5–13) years, respectively. From the clinical perspective, in 160 pregnancies (74.1%) women had a history of joint involvement, in 143 (66.2%) cutaneous involvement, in 68 (31.5%) haematological involvement, in 35 (16.2%) serositis and in 12 (5.5%) history of neuropsychiatric involvement. According to the study exclusion criteria, none had a history or present kidney involvement. In 10.8% of cases the disease was active at the first evaluation during pregnancy, and in active patients the median SLEDAI score was 5 (IQR 4–6).

As far as the serological profile is concerned, over the course of the disease, in all cases but one (99.5%) were patients ANA-positive, 50.5% anti-double stranded(ds) DNA, 49.5% anti-Ro, 19.4% anti-La, 6.9% anti-Nuclear Ribonucleoprotein (RNP) and 5.1% anti-Sm positive. According to the study exclusion criteria, none had current or history of positive aPL antibodies.

In 111 pregnancies (51.4%) patients received glucocorticoids during pregnancy (median daily dose of 5 mg

Table 1 Baseline characteristics of pregnancies

	All (N=216) n (%)	No low-dose acetylsalicylic acid (n=134), n (%)	Low-dose acetylsalicylic acid (n=82), n (%)	P value*
Age at pregnancy, years†	32 (30–36)	33 (29–37)	32 (30–36)	0.75
Disease duration†	9 (5–13)	8 (4–13)	9 (6–13)	0.26
Joint involvement‡	160 (74.1)	98 (73.1)	62 (75.6)	0.75
Cutaneous involvement‡	143 (66.2)	85 (63.4)	58 (70.7)	0.30
Haematological involvement‡	68 (31.5)	37 (27.6)	31 (37.8)	0.13
Serositis‡	35 (16.2)	21 (15.7)	14 (17.1)	0.84
Hypertension	8 (3.8)	7 (5.3)	1 (1.2)	0.26
Obesity	6 (3.2)	5 (4.3)	1 (1.3)	0.41
Smoking	2 (1.8)	2 (3.4)	0 (0.0)	0.50
First pregnancy	96 (45.7)	57 (43.8)	39 (48.8)	0.57
Assisted reproduction techniques	3 (2.1)	1 (1.3)	2 (3.0)	0.60
Hydroxychloroquine§	141 (65.3)	81 (60.4)	60 (73.2)	0.07
Glucocorticoids§	111 (51.4)	66 (49.3)	45 (54.9)	0.48
Azathioprine§	24 (11.1)	16 (12.0)	8 (9.8)	0.66
Ciclosporin A§	4 (1.9)	0 (0.0)	4 (4.9)	0.04
Active disease at first visit	22 (10.8)	16 (12.5)	6 (7.9)	0.36
SLEDAI at first visit†	2 (0–2)	2 (0–3)	2 (0–2)	0.28
Disease flares during pregnancy	26 (12.3)	17 (12.8)	9 (11.5)	0.83

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
Number of missing data: active disease at first visit: 12; SLEDAI at first visit: 16; hypertension: 5; obesity: 26; smoking: 103; first pregnancy: 6; medically assisted procreation: 73; disease flares during pregnancy: 5.
*P values from Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.
†Median (IQR).
‡At any time during the disease course.
§During pregnancy.

prednisone equivalent/day), in 141 (65.3%) women were on hydroxychloroquine, in 24 (11.1%) on azathioprine and in 4 (1.9%) on ciclosporin A.

In 82 pregnancies (38.0%) patients received LDASA during pregnancy; no differences in terms of age at conception and disease duration, clinical manifestations, comorbidities and disease flare during pregnancy were observed between cases on LDASA with respect to cases in which patients did not take LDASA during pregnancy. As far as concomitant therapies are concerned, a slightly higher percentage of patients on LDASA were also on hydroxychloroquine (73.2% vs 60.4%, p=0.07) or on ciclosporin A (4.9% vs 0%, p=0.04), while no differences were observed for glucocorticoids and azathioprine (table 1).

Pregnancy outcomes

Overall, APO was reported in 65 pregnancies (30.1%); in particular, pre-eclampsia was observed in 13 pregnancies (6.1%) and occurred before 34 gestational weeks in 7 cases (3.2%), IUFD in 3 (1.4%), IUGR in 12 (5.6%), very low birth weight in 13 (6.1%) and severe preterm birth in 11 pregnancies (5.1%). A detailed description of all pregnancy complications is reported in table 2. No significant association was observed between hypertension and pre-eclampsia: among 8 women with hypertension, 1 had pre-eclampsia, while among 203 women without hypertension 12 had pre-eclampsia (Fisher's exact test p=0.37). Of note, during pregnancy, in 12.3% of cases a disease flare occurred.

Interestingly, the frequency of all complications was similar in pregnancies of patients on LDASA and of patients who did not take LDASA during pregnancy.

When the correlation structure of the data was properly accounted for using mixed-effect logistic model, there was no evidence of association of the composite outcome with LDASA administration (unadjusted OR=1.37, 95% CI 0.39 to 4.76, p=0.62); the adjustment for potential confounders did not materially change the result (adjusted OR=1.19, 95% CI 0.37 to 3.81, p=0.77).

DISCUSSION

In this study we described the outcomes of pregnancies in a particular subgroup of patients with SLE without evidence of aPL and history or current nephritis. We aimed to test whether LDASA could have a protective role against APO in this highly selected population without the classic risk factors for pregnancy complications. Thus, the study aimed to address a clinical issue which is raised

Table 2 Pregnancy outcomes

	All (N=216) n (%)	No low-dose acetylsalicylic acid (n=134) n (%)	Low-dose acetylsalicylic acid (n=82) n (%)	P value*
Gestational diabetes	3 (2.1)	1 (1.3)	2 (3.0)	0.60
Pre-eclampsia	13 (6.1)	11 (8.3)	2 (2.4)	0.14
Early-onset pre-eclampsia (<34 weeks)	7 (3.2)	6 (4.4)	1 (1.2)	0.90
Intrauterine fetal death	3 (1.4)	3 (2.2)	0 (0.0)	0.29
Intrauterine growth restriction	12 (5.6)	7 (5.3)	5 (6.2)	0.77
Gestational weeks at delivery†	39 (37–40)	39 (37–40)	39 (37–39)	0.55
Preterm delivery	40 (18.9)	23 (17.7)	17 (20.7)	0.59
Birth weight <2500 g	33 (15.6)	19 (14.4)	14 (17.5)	0.56
Birth weight <1500 g	13 (6.1)	11 (8.3)	2 (2.5)	0.14
Size for gestational age				0.09
Small	23 (11.0)	10 (7.7)	13 (16.5)	
Appropriate	182 (87.1)	118 (90.8)	64 (81.0)	
Large	4 (1.9)	2 (1.5)	2 (2.5)	
Composite outcome‡	65 (30.1)	38 (28.4)	27 (32.9)	0.54

Number of missing data: gestational diabetes: 74; pre-eclampsia: 2; intrauterine fetal death: 0; intrauterine growth restriction: 2; gestational week: 6; preterm delivery: 4; birth weight: 8; birth weight <2500 g: 4; birth weight <1500 g: 3; size for gestational age: 7.
*P values from Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.
†Median (IQR).
‡Composite outcome: at least one of pre-eclampsia, intrauterine fetal death, intrauterine growth restriction, preterm delivery, birth weight <2500 g and small for gestational age.

very frequently in clinical practice and for which the available literature does not provide a clear and definite answer: should we prescribe LDASA to all patients with SLE during pregnancy?

As a matter of the fact, a recent study from the Systemic Lupus International Collaborating Clinics (SLICC) cohort showed that LDASA was prescribed in only 25% of lupus pregnancies despite the presence of traditional risk factors for pre-eclampsia.[15]

The first important result that emerged from this study is that the incidence of severe obstetric complications in this particular population is low; in particular, pre-eclampsia was observed in 6.1% of patients, an incidence significantly lower than that observed in unselected SLE cohorts and similar to the frequency observed in the general population.[16–19] The incidence of pre-eclampsia in our cohort was also lower than that expected in high-risk pregnancies, where it is around 9%.[20]

The most frequent obstetric complication was preterm delivery, observed in 18.9% of pregnancies; however, severe preterm delivery was reported in a minority of cases. It is important to note that these patients were strictly monitored and most pregnancies were planned, and these aspects could have had an impact on the low number of severe adverse events.

Our results are in line with previous findings on stable patients with SLE without active nephritis or prednisone >20 mg, as in the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study, where no difference in per cent of LDASA use in patients with and without APO was reported.[2] While the study did not restrict to those without aPL or nephritis as in our analysis, the importance of a good control of disease activity was stressed similarly.

The second aspect that emerged from this study is that LDASA does not seem to have a significant impact on the occurrence of obstetric complications in this type of patients; indeed, the frequency of the composite outcome APO and of each adverse outcome is similar in patients on LDASA and not.

This is in line with literature data on the general population showing that the relative risk reduction of pre-eclampsia with LDASA is modest and strongly related to the baseline, individual pre-eclampsia risk.[8 21] It may therefore be assumed that the sample size of our study is not sufficient to detect the beneficial effect of LDASA in this type of patient at low risk of complications.

Moreover, a possible bias by indication should be considered; indeed, we can assume that LDASA was probably administered to patients at increased risk of pregnancy complications, at least according to physician judgement.

However, it is interesting to note that pre-eclampsia had a frequency of 2.4% in patients taking LDASA, while those not taking LDASA had 8.3%. Although this difference is not statistically significant, probably due to the low

number of observations included, this could suggest a protective effect of LDASA against the hypertensive disorders of pregnancy. On the other hand, chronic hypertension was more frequent, even if not significantly, in the control group than in the LDASA group (5.2% vs 1.2%); this comorbidity represents a well-known major risk factor for pre-eclampsia warranting the intake of LDASA irrespective of the diagnosis of SLE.

Thus, based on these findings, patients with SLE without aPL nor lupus nephritis seem to have a low risk of severe obstetric complications (especially pre-eclampsia) and LDASA treatment does not provide a significant advantage over these complications.

On the other hand, it should also be emphasised that a robust body of evidence showed no significant haemorrhagic risk or fetal risk associated with LDASA use during pregnancy. Thus, in the individual risk–benefit assessment, the potential protection from pregnancy complications seems to outweigh the risk of adverse events.[8 22] Unfortunately, we did not assess haemorrhagic complications that occurred in our pregnancies.

This study has some limitations. First of all, it is a retrospective analysis and the physician's judgement has a strong weight in the study. Indeed, we did not observe any cluster of risk factors in patients who received LDASA, but still it is not possible to reproduce the clinical reasoning made by the physician (or the multidisciplinary team) during preconception counselling.

However, our data derived from the real-life practice of seven European referral centres for pregnancy in SLE and were carefully collected; thus, good standardisation among the centres is expected. The second limitation is related to the small sample size and the resulting small number of obstetric complications, limiting the statistical analysis.

On the other hand, to the best of our knowledge, this is the first study to assess the impact of LDASA in a selected and homogeneous population of patients with SLE with a low-risk profile for obstetric complications.

In conclusion, these data highlight the importance of a careful individual risk assessment for pregnancy complications in patients with SLE, hopefully in the setting of a preconceptional counselling. Moreover, these data encourage a shared decision-making process between patients, rheumatologists and obstetricians, taking into account disease-related and non-disease-related factors.

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Contributors CT and DZ contributed to the conception and design of the study, to the acquisition and interpretation of data, and were responsible for writing the manuscript. IH, MG, ML, LC, AB, FC, JM, FALS, FM, EE, RE, EB, MP, LA, LAC, GZ, MG, LI, AT, AD and RF actively contributed to the acquisition of data and drafting of the manuscript. LB and MF were responsible for data analysis and contributed to the drafting of the manuscript. MM contributed to the conception and design of the study and to the acquisition of data. MM was also responsible for the interpretation of data, contributed to the drafting of the manuscript and was responsible for the overall content as the guarantor. All authors have read and approved the final version of the article.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by Comitato Etico Area Vasta Nord Ovest (approval number: 13660) and performed according to the principles of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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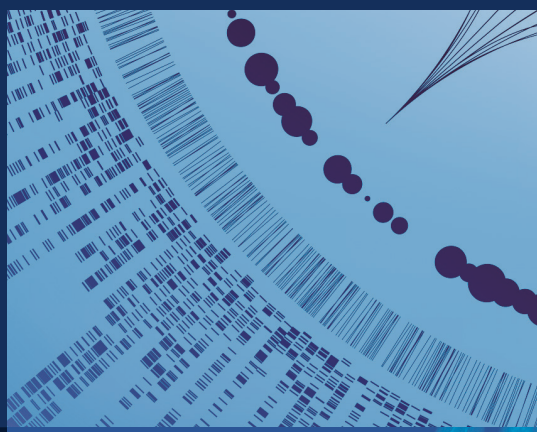

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POS0701 ANIFROLUMAB, AN ANTI-INTERFERON-A RECEPTOR MONOCLONAL ANTIBODY IN SYSTEMIC LUPUS ERYTHEMATOSUS- A META ANALYSIS

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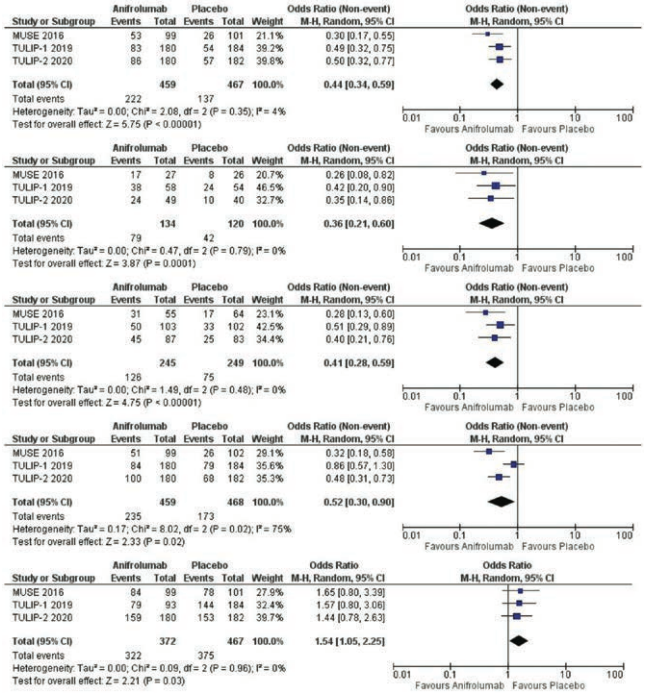
Background: Type I interferons such as Anifrolumab have been implicated in Systemic lupus erythematosus (SLE) pathogenesis on the basis of increased interferon-stimulated gene expression and genetic susceptibility. Little is known regarding its efficacy and safety profile.

Objectives: To assess the efficacy and safety of Anifrolumab in patients with SLE.

Methods: Electronic databases (PubMed, Embase, Scopus, Cochrane) were searched from inception until December 15th, 2020. Unadjusted odds ratios (OR) were calculated from dichotomous data using Mantel Haenszel (M-H) random-effects with statistical significance to be considered if the confidence interval excludes 1 and p<0.05. The primary outcome of interest was British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA). Secondary outcomes included the proportion of patients who achieved an SLE responder index of 4 (SRI-4) reduction of 50% or more in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), reductions in the glucocorticoid dose and adverse effects.

Results: A total of three studies[1,2,3] with 839 participants (Anifrolumab=372, Placebo=467) were included in our analysis. Follow-up duration was at week 52. A statistically significant different was observed in the Anifrolumab arm in terms of BICLA response (OR 0.44 95%CI 0.34-0.59;p<0.00001, I^2=4), ≥50% reduction in CLASI activity score (OR 0.36 95%CI 0.21-0.60;p=0.0001, I^2=0), glucocorticoid reduction (OR 0.41 95%CI 0.28-0.59;p<0.00001; I^2=0) and SRI-4 response (OR 0.52 95% CI 0.30-0.90; p=0.02, I^2=75). However, Adverse events were less likely in the placebo arm as compared to Anifrolumab (OR 1.54 95%CI 1.05-2.25; p=0.03; I^2=0).

Conclusion: Anifrolumab was found to be more effective than placebo for the management of SLE, but may also cause more severe adverse effects.



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POS0702 PREGNANCY IN SLE PATIENTS TREATED WITH BELIMUMAB: EXPERIENCE FROM 3 ITALIAN CENTERS

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Background: Belimumab (BEL) is a monoclonal antibody approved for SLE treatment but few data are available about its use before or during pregnancy.

Objectives: Our study aims to describe pregnancies in SLE patients who have discontinued BEL before conception, at positive pregnancy test or during pregnancy.

Methods: Data from prospectively-followed pregnancies (2014-2020) in SLE patients treated with BEL in 3 Italian centers where retrospectively collected, focusing on maternal disease activity, obstetric and neonatal outcome. Continuous data are expressed as median [min-max].

Results: Thirteen SLE pregnancies were analyzed (median age at conception 32 [24-41] years; 77% spontaneous, 69% primigravidae). All patients had positive ANA and anti-dsDNA antibodies; 4 had anti-Ro antibodies (31%); 4 had anti-phospholipid antibodies (aPL; 1 single, 2 double and 1 triple positivity). Seven patients (54%) had a history of lupus nephritis (LN); 2 patients (15%) had a concomitant diagnosis of antiphospholipid syndrome (1 thrombotic-APS and 1 thrombotic+obstetric-APS).

Ten (77%) pregnancies were planned and the use of BEL with regard to pregnancy was agreed with the patient during preconception counseling. At preconception visit, 8 patients were in remission while 5 had active disease (median SLEDAI 3 [0-8]).

BEL (11 intravenous, 2 subcutaneous) was stopped in 2 cases before conception, in 7 at positive pregnancy test and in 4 during pregnancy (2 at 11th week, 1 at 22nd, 1 at 24th); median duration of treatment at discontinuation was 29 [4-68] months. Other treatments during pregnancy were: oral prednisone in 12 cases (92%); intravenous methylprednisolone in 1 (8%); hydroxychloroquine in 10 (77%); chloroquine in 1 (8%); azathioprine in 5 (39%); calcineurin inhibitors in 5 (39%); low-dose acetylsalicylic acid in 10 (77%); low molecular weight heparin in 9 (69%).

Three flares occurred during the 3rd trimester in patients who stopped BEL at positive pregnancy test.

Live-births occurred in 92% of the pregnancies. A patient with thrombotic+obstetric-APS and LN, underwent assisted reproductive technology (embryo donation) and developed eclampsia (25thweek), an urgent cesarean section was performed and the newborn died after 3 days. One pre-eclampsia occurred in a patient with history of LN, double aPL positivity and active disease. One miscarriage at 11th week occurred; no early miscarriages (<10th week) were recorded. Pregnancy complications and outcomes are reported in Table 1.

No malformations were recorded. Two newborns were transferred to the Intensive Care Unit (1 for milk protein intolerance and 1 for desaturation).

Table 1. Pregnancy complications and outcomes according to the timing of discontinuation of BEL.

	BEL STOPPED PRECONCEPTIONALLY (2)	BEL STOPPED AT POS PREGNANCY TEST (7)	BEL STOPPED DURING PREGNANCY (4)
Pre-eclampsia	0/2	0/7	1/4 (25%)
Eclampsia	0/2	0/7	1/4* (25%)
Gestational Diabetes	0/2	1/7 (14%)	0/4
IUGR	0/2	1/7 (14%)	1/4* (25%)
pPROM/PROM	0/2	0/7	1/4 (25%)
Live birth	***1/2 (50%)***	***7/7 (100%)***	***4/4 (100%)***
Severe pre-term birth (≤ 34thweek)	0/2	0/7	1/4* (25%)
Late pre-term birth (35th- 37thweek)	0/2	3/7 (43%)	0/4
Small for Gestational age neonate	0/2	4/7 (54%)	1/4 (25%)
Late miscarriage (>10thweek)	***1/2 (50%)***	0/7	0/4
Perinatal death	0/2	0/7	***1/4* (25%)***

IUGR: IntraUterine Growth Restriction; PROM: Premature Rupture of Membrane; pPROM: pretermPROM;*in the same patient (history of thrombotic and obstetric-APS and lupus nephritis) who underwent Assisted Reproductive Technologies (embryo donation).

Eight newborns received vaccinations according to national schedule (missing data for 3). Five newborns were breastfed, 1 received formula milk and 5 mixed-feeding. BEL was resumed in 7/13 patients after pregnancy (in 4 cases for flare), after a median period of 5 [4-22] months.

Conclusion: While more data are needed, this small series suggests that BEL might be a therapeutic option for SLE patients during pregnancy planning, similarly to other biological drugs used in chronic forms of arthritis.

Disclosure of Interests: None declared

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POS0703 CARDIAC ADVERSE EFFECTS OF LONG-TERM USE OF HYDROXYCHLOROQUINE IN SYSTEMIC LUPUS ERYTHEMATOSUS. SINGLE UNIVERSITY CENTER STUDY OF 109 PATIENTS

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Background: Hydroxychloroquine (HCQ) is a widely used drug especially in connective tissue disorders such as Systemic Lupus Erythematosus (SLE). Cardiac adverse effects of long-term use of HCQ remains controversial.

Objectives: To assess cardiac adverse effects of long-term use of HCQ in SLE.

Methods: Observational single center study of 109 patients with SLE treated with HCQ for more than 3 months. The main outcomes were cardiac structural and conduction disorders in a 12-lead electrocardiogram and/or echocardiogram at baseline and during HCQ treatment.

Results: We studied 109 patients (95 women/14 men; mean age 66.9±14.7 years). Main cardiovascular history was hypertension (n=61, 56.0%), diabetes mellitus (n=16, 14.7%) and renal impairment (n=11, 10.1%). HCQ was used for 11.7±8.9 years. Initial median SLE Disease Activity Index 2000 (SLEDAI-2K) was 7 [3.75-11]. At baseline, 27 (24.8%) patients had conduction disorders and 15 (13.7%) had structural abnormalities: Most prevalent cardiac alterations were Left Anterior Fascicular Block (LAFB) (n=9, 8.3%), left ventricular hypertrophy (n=9, 8.3%) and right bundle branch block (n=8, 7.3%). After 11.7±8.9 years of follow-up (mean HCQ cumulative dose: 1042.2±267.5 g; median SLEDAI-2K 1 [0-4]), there was a significant increase in conductions disorders (n=41, 37.6%, p=0.011) and in LAFB (n=16, 14.7%, p=0.021). There was no statistically significant increase in structural abnormalities (n=21, 19.7%, p=0.629).

Table 1. Main cardiac abnormalities at baseline and after follow-up.

	Baseline	After follow-up	*p*
Conduction disorders, n (%)	27 (24.8)	41 (37.6)	0.011
Left anterior fascicular block	9 (8.3)	16 (14.7)	0.021
Right bundle branch block	7 (6.4)	8 (7.3)	1.0
Atrioventricular block	4 (3.6)	11 (10.1)	0.092
Incomplete right bundle branch block	4 (3.6)	5 (4.6)	1.0
Short PR interval	2 (1.8)	4 (3.7)	0.5
Prolonged QT corrected interval	2 (1.8)	4 (3.7)	0.625
Left bundle branch block	1 (0.9)	5 (4.6)	0.125
Atrial Fibrillation	1 (0.9)	5 (4.6)	0.219
Structural abnormalities, n (%)	15 (13.7)	21 (19.7)	0.629
Ventricular hypertrophy	9 (8.3)	9 (8.3)	1.0
Atrial enlargement	6 (5.5)	13 (11.9)	0.096

Main cardiac abnormalities at baseline and after 11.7±8.9 years of follow-up are summarized in Table 1. Time of occurrence of cardiac adverse effect in relation to HCQ cumulative dose is shown in Figure 1.

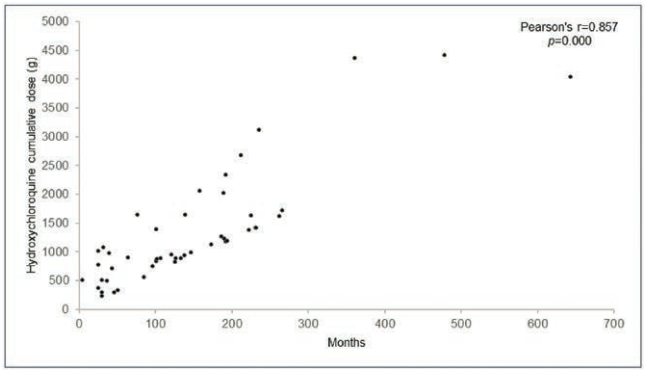

Figure 1. Time of occurrence of cardiac adverse effect in relation to hydroxychloroquine cumulative dose.

Conclusion: Conduction disorders were more prevalent than structural abnormalities. Patients with SLE treated with HCQ had a significant increase in LAFB. Use of electrocardiogram and/or echocardiogram may be helpful in monitoring cardiac adverse effects.

Disclosure of Interests: Alba Herrero-Morant: None declared, Adrián Margarida-de Castro: None declared, Raquel Pérez-Barquín: None declared, Jon Zubiaur-Zamacola: None declared, Miguel Á. González-Gay Speakers bureau: AbbVie, Pfizer, Roche, Sanofi, Lilly, Celgene and MSD, Grant/research support from: AbbVie, MSD, Jansen and Roche, Ricardo Blanco Speakers bureau: AbbVie, Pfizer, Roche, Bristol-Myers, Janssen, Sanofi, Lilly and MSD, Grant/research support from: AbbVie, MSD, and Roche

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POS0704 LONG-TERM CLINICAL OUTCOMES OF PATIENTS WITH LUPUS NEPHRITIS TREATED WITH AN INTENSIFIED B-CELL DEPLETION PROTOCOL: A PROSPECTIVE STUDY

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Background: B cells play a key role In the pathogenesis of Lupus Nephritis (LN).

Objectives: we aim to investigate the safety and efficacy of an intensified B-cell depletion induction therapy (IBCDT)without immunosuppressive maintenance regimen compared to standard of care in biopsy-proven LN.

Methods: Thirty patients were administered an IBCDT (4 weekly Rituximab 375mg/m2 and 2more doses after 1&2 months;2 infusions of 10 mg/kg cyclophosphamide (CYC),3 methylprednisolone pulses), followed by oral prednisone (tapered to 5 mg/day by the 3rd month). No immunosuppressive maintenance therapy was given. Thirty patients matched for LN class and age were selected as controls: 20 received 3 methylprednisolone pulses days followed by oral prednisone and mycophenolate mofetil (MMF) 2-3 g/day, while 10 were given the Euro Lupus CYC.

Results: At 12 months, complete renal remission was observed in 93% of patients on IBCDT, in 62.7% on MMF, and in 75% on CYC (p=0,03); the dose of oral prednisone was lower in the IBCDT group (mean±SD 2.9±5.0mg/dl) than MMF (10.5±8.0 mg/day,p<0.01) or CYC group (7.5±9.0mg/day,p<0.01). Mean follow-up after treatment was 44.5 months (IQR 36–120months), 48.6 months (IQR36–120months), and 45.3 (IQR36–120months) for IBCDT, MMF and CYC, respectively. At their last follow-up visit, we observed no significant differences in proteinuria and serum creatinine, nor in the frequency of new flares among the three groups.

Conclusion: In biopsy proven LN, the IBCDT without further immunosuppressive maintenance therapy was shown to be as effective as conventional regimen of MMF or CYC followed by a 3-year maintenance MMF regimen. Moreover, the use of IBCDT was associated with a marked reduction of glucocorticoid cumulative dose.

Disclosure of Interests: None declared

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Allegato 11

ABSTRACT NUMBER: 0961

The Use of Belimumab Before and During Pregnancy in Patients with Systemic Lupus Erythematosus: An Italian Multicenter Case-series

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SESSION INFORMATION

Date: Sunday, November 13, 2022

Session Type: Poster Session B

Title: Reproductive Issues in Rheumatic Disorders Poster

Session Time: 9:00AM-10:30AM

Background/Purpose: Belimumab (BEL) is an anti-BLyS monoclonal antibody approved for SLE treatment. As few data about BEL use with regard to pregnancy are available, the aim of this study is to describe pregnancies exposed to BEL either preconceptionally or during pregnancy.

Methods: Data of prospectively-followed pregnancies (2014-2021) in SLE patients treated with BEL in 6 Italian centers where retrospectively collected, focusing on disease activity and outcome. Continuous data were reported as median (interquartile range).

Results: Twenty-one pregnancies in 21 SLE patients were collected (median age at conception: 34 [31-38] years; 13 in primigravidae (62%); 16 planned (76%); 18 spontaneous (86%)).

BEL (14 intravenous, 7 subcutaneous) was stopped in 3 cases preconceptionally, in 9 at positive

pregnancy test and in 9 during pregnancy (4 during the 1st trimester, 3 during the 2nd trimester and 2 during the 3rd trimester) (Table 1). The use of BEL during pregnancy had been agreed with the patient during preconception counselling.

Other treatments during pregnancy were: prednisone (90%); antimalarials (81%); azathioprine (48%); calcineurin-inhibitors (29%); low-dose acetylsalicylic acid (86%); low molecular weight heparin (57%).

At preconception visit, the median SLEDAI was 4 [2-4].

Three pregnancies had a flare (1 during the 2nd and the 3rd trimester; 2 during the 3rd trimester), all in patients who withdrew BEL at positive pregnancy test.

Live-births were 86%.

Two miscarriages (at 7th and 11th week) and 1 intrauterine fetal death (at 37th week; 21-trisomy with atrio-ventricular defect) occurred. One perinatal death occurred (in a patient with thrombotic+obstetric APS and lupus nephritis who underwent heterologous assisted reproductive technology -embryodonation- and developed eclampsia with cerebral haemorrage at 25thweek; an urgent cesarean section was performed and the newborn died after 3 days).

Two pre-eclampsia were registered: 1 at 38th week in a patient with history of lupus nephritis, double aPL positivity and active disease and 1 at 33th week in a patient with cardiovascular risk factors (hypertension, obesity, cigarette smoke) and a history of pre-eclampsia in a previous pregnancy.

Four newborns were hospitalized in Intensive Care Unit (1 milk protein intolerance; 1 desaturation; 2 prematurity). One urine infection with sepsis occurred at 2 months in a baby with calico-pyelic and ureteral dilatation at birth (pre-term birth).

Eleven newborns received vaccinations according to national schedule (7 missing data).

Conclusion: In this case series, the use of BEL during pregnancy was discussed with some patients with a severe disease phenotype and at high risk of having a flare during pregnancy, in order to favor disease remission. While more data are needed, the timing of discontinuation should be individualized according to the single patient's characteristics and preferences, with a risk-benefit evaluation.

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Stopping bDMARDs at the beginning of pregnancy is associated with disease flares and preterm delivery in women with rheumatoid arthritis

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Objectives: Women with Rheumatoid Arthritis (RA) can experience flares during pregnancy that might influence pregnancy outcomes. We aimed at assessing the disease course during pregnancy and identifying risk factors for flares.

Methods: Data about prospectively-followed pregnancies in RA were retrospectively collected before conception, during each trimester and in the post-partum period. Clinical characteristics, disease activity (DAS28-CRP3), medication use, and pregnancy outcomes were analysed with regard to disease flares.

Results: Among 73 women who had a live birth, 64 (88%) were in remission/low disease activity before conception. During pregnancy, a flare occurred in 27 (37%) patients, mainly during first and second trimester. Flares during pregnancy were associated with the discontinuation of bDMARDs at positive pregnancy test (55% of patients with flare vs. 30% of patients with no flare, p 0.034, OR 2.857, 95% CI 1.112–8.323) and a previous use of >1 bDMARDs (33% of patients with flare vs. 10% of patients with no flare, p 0.019, OR 4.1, 95%CI 1.204–13.966). Preterm pregnancies were characterised by higher values of CRP [10 mg/L (5–11) vs. 3 mg/L (2.5–5), p 0.01] and DAS28-CRP3 [4.2 (1.9–4.5) vs. 1.9 (1.7–2.6), p 0.01] during the first trimester as compared with pregnancies at term. Preterm delivery was associated with the occurrence of flare during pregnancy (flare 27% vs. no-flare 7%, p 0.034, OR 4.625, 95%CI 1.027–20.829).

Conclusion: Preterm delivery in RA patients was associated with flares during pregnancy. Flares occurred more frequently after the discontinuation of bDMARDs at positive pregnancy test. Women with aggressive RA on treatment with bDMARDs

should be considered as candidates for continuing bDMARDs during pregnancy in order to reduce the risk of flare and adverse pregnancy outcomes.

KEYWORDS

rheumatoid arthritis, pregnancy, bDMARDs, TNF inhibitors, disease activity, disease flare, pregnancy outcomes

Introduction

In 1938, Philip Hench described a temporary improvement in Rheumatoid Arthritis (RA) during pregnancy, followed by a post-partum flare (Hench, 1938). Retrospective studies between 1938 and the 1980s, lacking objective measures of disease activity, described improvement in up to 90% of RA women during pregnancy followed by post-partum flares in about 80% (Hazes et al., 2011). In these studies, RA women were not treated with specific RA drugs, maybe occasionally with glucocorticoids.

A systematic review of more recent prospective studies, in which objective indices of disease activity were used, found that 60% of patients with RA improve during pregnancy and 47% relapse after delivery (Jethwa et al., 2019). Only two studies included RA women who were on treatment with conventional disease-modifying anti-rheumatic drugs (cDMARDs) (de Man et al., 2008; Förger et al., 2012) and none of the women in the included studies used tumor necrosis factor inhibitors (TNFi) or other biological DMARDs (bDMARDs) during pregnancy.

Nowadays, an increasing number of RA patients can reach remission or low disease activity thanks to the treat-to-target approach (T2T) with cDMARDs and bDMARDs. Being free of disease-related disability, young women living with RA can pursue their family plans and seek for a pregnancy. However, the management of treatment, especially bDMARDs, in relation to pregnancy has been debated in the last decade. The past general approach has been withdrawal of bDMARDs at positive pregnancy index, in order to avoid exposure during the early phases of pregnancy. As reassuring data about the use of bDMARDs during pregnancy accumulated, mostly about TNFi, recommendations from national and international societies have underlined their possible use during pregnancy, in the presence of a favorable benefit-risk ratio in the individual case (Flint et al., 2012; Gotestam Skorpen et al., 2016; Sammaritano et al., 2020).

The aim of this study was to assess the disease course of RA during pregnancy and pregnancy outcomes in relation to medication use and to identify possible risk factors for flares during pregnancy.

Materials and Methods

Patients

Data about RA pregnancies were retrospectively collected before conception and during each trimester and post-partum period. All the patients were prospectively followed at the multidisciplinary Pregnancy Clinic for Rheumatic Diseases at the University Hospital in Brescia between 2000 and 2018. Patients fulfilled the 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis (Aletaha et al., 2010). All the patients signed a written informed consent. The study was approved the local Ethics Committee (Code N. 0025589—NP n. 1,647).

Time points and clinical assessment

Data collection was performed at five time points: preconception visit (3–6 months before conception), during each trimester of pregnancy (first: 8–12 weeks of gestation, second: 18–24 weeks, third: 30–36 weeks), and up to 6 months after delivery.

The standard management consisted of a routine physical examination, assessment of diseases activity including the measurement of C-reactive protein (CRP) and recording of the current medication and complications. Presence of rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), and bone erosions at X-rays were ascertained from the patients' medical records.

Assessment of disease activity and flare definition

Disease activity was assessed using the three-variable Disease Activity Score in 28 joints with CRP (DAS28-CRP3) since this score was shown to perform best in pregnancy (de Man et al., 2007). The mean disease activity scores were calculated at each time point. As previously described by *de Man et al.* (de Man et al., 2008), remission was defined as a DAS28-CRP < 2.6, according to the EULAR criteria, but using CRP instead of ESR. The proportions of women in clinical remission and with low, moderate, or high disease activity before pregnancy, during pregnancy, and after delivery were calculated.

As previously described by de Man et al. (de Man et al., 2008), flare was defined by an increase of DAS28-CRP3 between preconception visit and each time point >0.6 if the value was >3.2 or by an increase of DAS28-CRP3 >1.2 if the value was ≤3.2.

Assessment of pregnancy outcome

Data on pregnancy outcome included early miscarriages (<10th gestational week), intrauterine foetal death (>10th

gestational week), gestational age at delivery, mode of delivery, sex of the child, birth weight. Pregnancy complications were also recorded, including preterm deliveries (<37th gestational week), premature rupture of membranes (PROM), small for gestational age (SGA) babies (those with a birth weight below the 10th percentile for gestational age), and hypertensive disorders (gestational hypertension and pre-eclampsia). Data were retrieved from medical charts and by telephone interview when lacking. Mode of delivery was defined as spontaneous vaginal, induced vaginal, and caesarean section (elective or emergency).

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), whereas categorical variables as proportion and/or percentage. Mann-Whitney test for continuous variables and Fisher's exact test or Chi-square test for categorical variables were applied as appropriate. Logistic regression was applied for multivariate analysis. The model included those variables that had been associated with disease flare in the literature (e.g., negative prognostic factors such as ACPA or RF positivity) and variables related to drug exposure (e.g., stopping csDMARDs or bDMARDs) (see Table 2). p-values < 0.05 were considered as significant and Odds Ratio (OR) with 95% Confidence Interval (95% CI) was reported.

Results

Study cohort

A total of 83 pregnancies in 64 RA patients were identified. Eight (10%) pregnancies ended with early miscarriages (<10th gestational week), 1 (1%) with intrauterine foetal death (at 12th gestational week) and 1 (1%) with ectopic pregnancy.

The remaining 73 (88%) live-birth pregnancies in 63 patients (median age 35 years [IQR 30-38], median disease duration 68 months [IQR 30-159], positive ACPA 57%; positive RF 57%) were analysed. Eight women contributed with two live-birth pregnancies and one woman with three live-birth pregnancies.

Clinical, demographic, neonatal and breastfeeding features of 73 RA pregnancies are described in Table 1.

Disease course and medications

Before conception, 54 (74%) patients were in remission, 10 (14%) had low disease activity and 9 (12%) moderate disease activity. None of the patients had high disease activity. During pregnancy, the percentage of patients with moderate disease activity increased during the first (12, 16.7%) and second trimester (17.2%). One patient (1.4%) had high disease activity during second and third trimester. After delivery, 27 (37%) patients were in remission, 7 (9.6%) had low disease activity, 22 (30.1%) moderate disease activity and 4 (5.5%) high disease activity (Figure 1). Twenty-four (40%) patients experienced a flare.

Table 2 reports on the use of drugs during each trimester and post-partum period (presented as overall use and start/resume of single drugs). Before conception, 41 (56%) patients were on treatment with cDMARDs and 30 (41%) on bDMARDs. Particularly, 23/29 (80%) patients who had stopped bDMARDs at positive pregnancy test resumed it during pregnancy (11/29, 38%) or after delivery (12/29, 41%) due to disease flare. Of note, 35 pregnancies (48%) were treated with low-dose acetylsalicylic acid and 8 (11%) with prophylactic dose heparin for obstetric indication and/or antiphospholipid antibodies positivity.

No severe infections nor hospitalizations were observed. Women treated with bDMARDs during pregnancy and the post-partum period did not display a higher frequency of non-severe infections as compared to women treated with cDMARDs.

Risk of flare

During pregnancy, flares occurred in 27 (37%) patients: 13 (18%) during first trimester, 10 (14%) during second trimester, and 6 (9%) during third trimester. Two patients experienced more than one flare. During the post-partum period, a flare occurred in 24 (40%) patients (median week after delivery 12, IQR 6-18). Two post-partum flares were observed also in 2 out of 10 (20%) women whose pregnancies had ended into spontaneous miscarriage.

By comparing pregnancies with and without flares (Table 3), flares during pregnancy were associated with elevated CRP and active disease in the first trimester, previous use of more than one bDMARDs, and the discontinuation of bDMARDs at positive pregnancy test. Active disease during first trimester was the only variable significantly associated with flare at the multivariate analysis (p 0.01, OR 5.4, CI 95% 1.48–19.55) (Table 3). Patients positive for RF and/or ACPA and patients with erosive disease did not display a higher frequency of flares as compared to patients without these features.

Pregnancy and neonatal outcome

Among 73 live-birth pregnancies, twenty-one (29%) had at least one complication. There were 8 preterm deliveries, of which 3 occurring <34th gestational week; 12 PROM, of which

TABLE 1 Demographic, clinical, and neonatal characteristics of 73 pregnancies in patients with Rheumatoid Arthritis.

Age at conception (years), median (IQR)	35 (30-38)
Disease duration (months), median (IQR)	68 (30-159)
Positive RF	42 (57%)
Positive ACPA	42 (57%)
Bone Erosions	19/62 (30%)
History of > 1 cDMARD	20 (27%)
History of > 1 bDMARD	9 (12%)
Comorbidities on treatment	19 (26%)
Primigravida	26 (35%)
Preconception DAS28-CRP 3, median (min-max)	1.8 (1.1–4.1)
First trimester DAS28-CRP 3, median (min-max)	1.8 (1.1–5.9)
Second trimester DAS28-CRP 3, median (min-max)	1.9 (1.1–6.2)
Third trimester DAS28-CRP 3, median (min-max)	1.8 (1.1–5.2)
Post-partum period DAS28-CRP 3, median (min-max)	1.9 (1.1–6.2)
Gestational week at delivery, median (IQR)	39 (38–48)
Neonatal weight (grams), median (IQR)	3187 (2800–3500)
Breastfeeding	37 (50%)
Breastfeeding in LDA patients	23/37(62%)
Breastfeeding in no-LDA patients	12/21 (57%)
No breastfeeding due to maternal intake of non- compatible drugs	11 (15%)
No breastfeeding due to maternal choice	25 (35%)

Values indicate absolute numbers (percentage) unless otherwise stated.
ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DAS28-CRP3, disease activity score in 28 joints with CRP; DMARD, disease-modifying anti-rheumatic drug; bDMARD, biologic DMARD; cDMARD, conventional DMARD; GC, glucocorticoids; LDA, low disease activity; RA, rheumatoid arthritis; RF, rheumatoid factor.

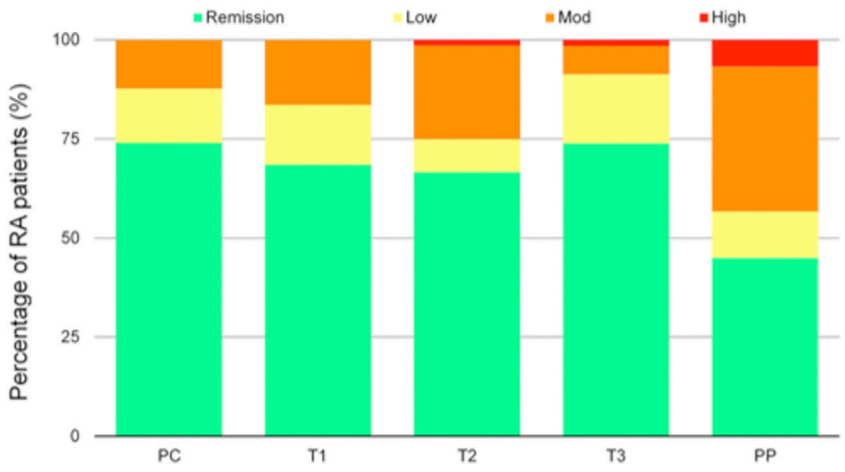

FIGURE 1
Disease activity according to Disease Activity Score in 28 joints (DAS28) during pregnancy and postpartum, classified as remission (DAS28 < 2.6), low disease activity (DAS28 2.6–3.2), moderate disease activity (DAS28 3.2–5.1), and high disease activity (DAS28 > 5.1). RA, rheumatoid arthritis; PC, preconception visit; T1 first trimester, T2 second trimester, T3 third trimester, PP post-partum.

TABLE 2 Overall exposure to anti-rheumatic drugs and changes of treatment during pregnancy and post-partum period (numbers refer to patients on treatment at each time point).

	PC	T1		T2		T3		POST-PARTUM	
PDN, mg/day, median (IQR)	5 (3.5–5)	5 (3.5–6.25)		5 (3.5–6.25)		5 (3.5–7.5)		5 (2.8–6)	
		overall	start/resume	overall	start/resume	overall	start/resume	overall	start/resume
HCQ, n	26	36	10	38	2	35	0	34	9
SSZ, n	8	5	3	5	0	4	0	6	2
Cy-A, n	3	3	0	3	0	3	0	3	0
MTX/LEF, n	3	0	0	0	0	0	0	7	4
ETA, n	16	4	3	5	2	5	0	10	5
CTZ, n	5	1	1	4	3	5	1	6	1
ADA, n	4	0	0	1	1	1	0	3	2
GOL, n	3	0	0	0	0	0	0	1	1
Other bDMARDs, n	2	0	0	0	0	0	0	1	1

ADA, adalimumab; bDMARD, biological Disease-modifying anti-rheumatic drugs; Cy-A, cyclosporine; CTZ, certolizumab pegol; ETA, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; IQR, interquartile range; LEF, leflunomide; MTX, methotrexate; PC, preconception visit; PDN, prednisone; SSZ, sulfasalazine; T1 first trimester, T2 second trimester, T3 third trimester.

TABLE 3 Risk factors for disease flare during pregnancy.

	RA pregnancies (*n*=73)				
	Flare	No flare	OR	95%CI	p value
Positive RF	19/27 (70%)	25/46 (50%)	1.9	0.7–5.4	0.17
Positive ACPA	21/27 (77%)	24/46 (52%)	1.8	0.6–6.3	0.14
Erosive disease	9/27(33%)	10/46(21%)	1.5	0.7–7.2	0.27
History of > 1 cDMARD	13/27 (48%)	26/46 (56%)	0.7	0.3–1.8	0.48
History of >1 bDMARD	9/27 (33%)	5/46 (10%)	4.1	1.2–13.9	0.02
Elevated CRP before pregnancy	4/27 (14%)	7/46 (15%)	0.96	0.2–3.7	0.96
Active disease 1st trimester	9/27 (33%)	2/46 (4%)	11	2.16–55	0.01[§*]
Elevated CRP 1st trimester	12/25 (48%)	7/44 (16%)	4.8	1.6–15	0.04[§]
GC before pregnancy	19/27 (70%)	26/46 (56%)	1.8	0.6–5.2	0.24
cDMARD stopped before pregnancy	1/27 (3%)	0/46 (0%)	1.03	0.96–1.2	0.18
cDMARD stopped at positive pregnancy test	6/27 (22%)	10/46 (21%)	1.02	0.32–3.2	0.96
bDMARD stopped before pregnancy	0/27 (0%)	2/46 (4%)	0.95	0.9–1.02	0.27
bDMARD stopped at positive pregnancy test	15/27 (55%)	14/46 (30%)	2.8	1.06–7.06	0.03[§]

*p-value (multivariate analysis): (p 0.01. OR 5.4. CI 95% 1.48-19.55).
[§]Variables included in the multivariate analysis.
"Before pregnancy" refers to the period from 20 weeks prior to conception until the positive pregnancy test.
ACPA, anti-citrullinated protein/peptide antibodies; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; GC, glucocorticoids; RA, rheumatoid arthritis; RF, rheumatoid factor; OR, odds ratio.

8 preterm; 10 SGA newborns. One pregnancy was complicated by gestational hypertension and no case of pre-eclampsia was observed. By comparing pregnancies with and without the above-mentioned complications, no difference was observed in the history of adverse pregnancy outcomes in previous pregnancies, disease activity during pregnancy, values of CRP during pregnancy, glucocorticoids/cDMARDs/bDMARDs use during pregnancy.

Pregnancies ended with preterm delivery were characterised by higher values of CRP and DAS28-CRP3 in the first trimester as compared with pregnancies at term (10 mg/L (5–11) vs. 3 mg/L (2.5–5), *p* 0.01; 4.2 (1.9–4.5) vs. 1.9 (1.7–2.6), *p* 0.01, respectively). Preterm delivery was associated with the occurrence of flare (flare 27% vs. no-flare 7%, *p* 0.034; OR 4.625, 95% CI 1.03–20.83).

Discussion

In the present study, we investigated the risk factors for disease flare during pregnancy in RA women who received preconception counselling and were mostly in good disease control at the time of conception (88% in remission or low disease activity at the time of conception, no patient with severely active disease). Flares during pregnancy and after delivery were observed in 37 and 40% of RA pregnancies, respectively. The occurrence of a flare during pregnancy was significantly associated with the withdrawal of bDMARDs (mostly TNFi) at positive pregnancy test. These results are concordant with other two studies. In 2015, Fischer-Betz et al. observed a flare in 16 (38%) pregnancies among 42 RA pregnancies. Women with RA who discontinued TNFi at conception displayed a high risk of flares during pregnancy, independently of known risk factors like RF and ACPA positivity and despite remission/low disease activity at conception (*p* 0.003 OR 8.2, 95% Cl 2.1–33.2) (Fischer-Betz et al., 2015). In 2017, *van den Brant et al.* observed disease flares in 29% of 75 pregnant RA women; the majority of flares occurred during the first trimester. Active disease and elevated CRP in early pregnancy along with the discontinuation of TNFi in the first trimester were identified as risk factors for flare (relative risk -RR 3.333, 95% CI 1.8–6.1, *p* 0.001) (van den Brant et al., 2017). More recently, *Förger et al.* showed that in RA patients with inactive disease, the discontinuation of TNFi before the 20th week of gestation did not result in active disease later in pregnancy as compared to continuing TNFi beyond the 20th week of gestation (Förger et al., 2019). However, it should be noted that patient-reported outcome measures were used to assess disease activity in this study and that the drugs were stopped later in gestation compared to the present study and to the above-mentioned studies (Fischer-Betz et al., 2015; van den Brandt et al., 2017).

The continuation of compatible drugs beyond conception and during pregnancy ensures a good control of maternal disease throughout pregnancy (Flint et al., 2012; Gotestam Skorpen et al., 2016; Sammaritano et al., 2020). As observed in this study, an active disease during the first trimester is a strong predictor of flare during pregnancy. On the other hand, low disease activity in the first trimester was shown to predict low disease activity or remission in the last trimester (Ince-Askan et al., 2017). Recent data from the PreCARA cohort showed that a modern treatment approach in pregnant RA patients, including T2T and the prescription of TNFi, yielded a low disease activity and remission during pregnancy, with 90.4% of patients achieving this target in the third trimester (Smeele et al., 2021).

In our study, flares occurred more frequently in patients previously treated with more than one bDMARDs. This finding suggests that patients with a more aggressive or difficult-to-treat disease have a higher risk of flaring up and need to continue compatible drugs beyond conception.

After delivery, women with RA are at risk of disease flare. Prospective studies before the year 2000 described high rates of postpartum disease worsening, ranging from 66 to 77% (Ostensen & Husby, 1983; Unger et al., 1983; Barrett et al., 1999). In a meta-analysis of five prospective studies from 2004 to 2013, a post-partum increase in disease activity was found in 46.7% of patients with RA (Jethwa et al., 2019). A recent study demonstrated that a tight control before pregnancy suppressed RA disease activity during pregnancy and in the postpartum period (Nakamura et al., 2021). In our cohort, 40% of patients experienced a flare. The progressive reduction of the rate of disease flares after delivery reflects a better management of RA over decades thanks to the use of csDMARDs and bDMARDs that can be continued during pregnancy and breastfeeding.

A good control of maternal disease activity is crucial not only to ensure a better RA course during pregnancy but also to favour a better pregnancy outcome. In this study, pregnancies that ended with a preterm delivery were characterised by higher values of CRP and DAS28-CRP3 in the first trimester as compared with pregnancies at term and they were associated with the occurrence of flare. These results are in agreement with a recent study conducted in 647 RA pregnant women between 2004 and 2017 (Smith et al., 2019). RA women had an increased risk of preterm deliveries versus the comparison group (RR 2.09, 95% CI 1.50–2.91), and an active disease at enrolment (aRR 1.58, 95% CI 1.10–2.27) and anytime during pregnancy (aRR 1.52, 95% CI 1.06–2.18) was associated with this complication (Smith et al., 2019). Another larger study carried on 440 RA pregnant women between 2005 and 2015 found that RA disease severity measured in early pregnancy was predictive of preterm delivery and SGA (Bharti et al., 2015), suggesting that tight control of disease activity in early pregnancy might improve birth outcomes. One retrospective study from 2014 showed no association between preterm deliveries and active disease at conception or throughout pregnancy (Langen et al., 2014). One might expect that the increased rate of preterm deliveries can be mediated through more glucocorticoid use to control disease flares, as this relationship has previously been documented in the literature (Smith et al., 2019). However, no association between preterm delivery and glucocorticoid use during pregnancy was observed in the present study. This finding could be accounted to the low dose of steroids (≤7.5 mg/day) used in our cohort (Table1). In our practice, pregnant women with active disease requiring dosages >7.5 mg were candidate to treatment with DMARDs,

particularly bDMARDs, with the aim of minimizing the possible maternal and foetal adverse events linked to the continuous use median dosages of steroids during pregnancy. No association was also found between cDMARDs and/or bDMARDs use and adverse pregnancy outcomes, confirming recent data (Tsao et al., 2018a).

As a limitation of this study, we must mention the use of EULAR response criteria using the DAS-28 with CRP instead of ESR. In fact, as demonstrated by De Man et al. (De Man et al., 2009), disease activity can be measured the most reliably during pregnancy with the DAS28-CRP-3, because ESR increases physiologically during pregnancy. Another limitation of the present study was the inclusion of two or three pregnancies occurring in the same patient. The inclusion of a second or subsequent pregnancy might introduce bias, since it may represent a selection bias for women who previously had a good experience with their RA course during and after pregnancy and/or a good experience with the outcome of the pregnancy. On the other hand, it has been demonstrated that RA disease course in subsequent pregnancies cannot be predicted based upon previous pregnancies (Ince-Askan et al., 2016). We included pregnancies from 2000 to 2018, a long period in which the management of RA during pregnancy has been changing. The low number of pregnancies in each historical period did not allow us to make a sub-analysis upon calendar year.

The management of RA has improved in the past 2 decades with the introduction of a T2T approach and new and effective treatment options. This resulted in more women desiring pregnancy. As several rheumatology international guidelines for medication use in pregnancy and breastfeeding stated (Flint et al., 2012; Gotestam Skorpen et al., 2016; Sammaritano et al., 2020), there are multiple medications that are considered compatible with pregnancy and they should be continued during pregnancy if necessary. Despite the growing evidence about the safety of most of anti-rheumatic medications in pregnancy and breastfeeding, a frequent discontinuation of medications for RA, particularly in the first trimester, has been recently observed (Rebić et al., 2020) and women with RA resulted more than 3 times as likely to discontinue bDMARDs compared to those with inflammatory bowel disease (Tsao, et al., 2018b). This difference could be due to the old and widely held perception that RA spontaneously improves during pregnancy.

As we demonstrated in this study, a large proportion of RA women can experience a flare during pregnancy despite the good control of their disease activity before conception. Stopping bDMARDs early in pregnancy increases the risk of developing a flare during pregnancy. This information should be addressed during preconception counselling of women with RA, especially those with aggressive and/or refractory forms (e.g., history of more than one bDMARDs) and they should be offered to continue treatment during pregnancy to ensure control of maternal disease and prevent adverse pregnancy outcomes, particularly preterm delivery.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by COMITATO ETICO—ASST SPEDALI CIVILI DI BRESCIA. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Author contributions: MC-G, FF, AT, and LA designed the study. MC-G, FC, DL, and A-GF organized the database. ML, FC, DL, A-GF, CB, IC, MF, MFR, RG, MG-L, CN, MT, AL, FR, CZ, SZ, FF, AT, and LA evaluated the patients and compiled the database. MC-G, A-GF, FF, AT, and LA wrote the manuscript. All authors reviewed the manuscript draft, read and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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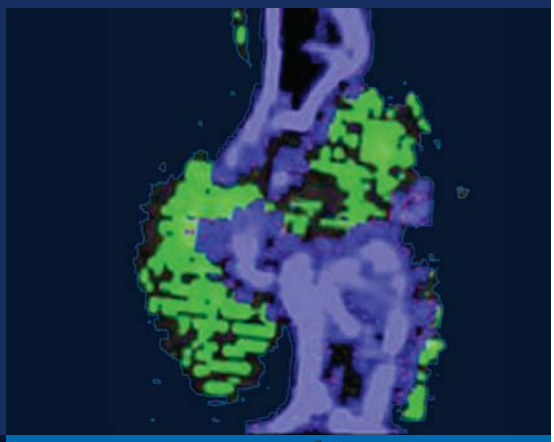

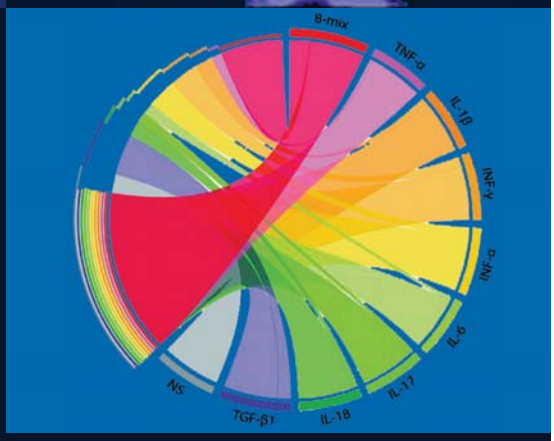

Abstracts

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POS0151

PREGNANCIES IN PATIENTS WITH SPONDYLOARTHRITIS: DATA FROM 2 EUROPEAN CENTERS.

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Background: There is growing interest in reproductive issues in patients with Spondyloarthritis (SpA) and Psoriatic arthritis (PsA).
Objectives: To describe a real-life cohort of prospectively-followed pregnancies in SpA and PsA patients, focusing on obstetric outcome and on flare during pregnancies and post-partum.
Methods: Data on SpA and PsA pregnancies prospectively-followed in 2 European pregnancy clinics from 2010 to 2021 were retrospectively analysed.
Disease activity was assessed using ASDAS-CRP or DAS28-CRP according to the main involvement (peripheral or axial). Disease flare was defined as the need to treatment modification (introduction or increase ≥5mg/day of prednisone, introduction of cDMARD or bDMARD). Miscarriages were excluded from the analysis of flares.
Results: Data on 122 pregnancies (53 PsA and 69 'other SpA': 39 axialSpA, 20 undifferentiated SpA, 6 IBD-related SpA, 4 reactive arthritis) in 102 patients (median age at conception: 34 [IQR: 31-36] years; median disease duration: 72 [24-132] months) were collected.
We recorded 98 (86%) live births and 16 (14%) miscarriages (8 missing data).
Cesarean section was performed in 15/98 (15%) cases. Median week of gestation at delivery was 39 [38-40]; 8 preterm births (<37 week of gestation) and 2 severe preterm births (<34 week of gestation) occurred. There was no difference between PsA or 'other-SpA' concerning pregnancy outcome and route of delivery.
Fourty-two pregnancies (40%) had at least 1 flare during pregnancy; 7 pregnancies had more than 1 flare. Overall, there were 13, 24 and 12 flares in the 1st, 2nd and 3rd trimester, respectively.
A higher frequency of patients with axial involvement was observed in the 'flare' group as compared to pregnancies without flare (83% vs 59%, p=0.02) (Table 1).

Table 1. Comparison between 'flare' and 'without flare' groups.

	FLARE (42)	WITHOUT FLARE (64)	*p*
Age at conception (years)	33 (31-37)	33 (31-35)	0.88
Disease duration at conception (months)	71 (24-120)	60 (24-137)	0.74
PsA	13 (31%)	31 (48%)	0.11
'Other SpA'	29 (69%)	33 (52%)	0.11
Axial involvement	**35 (83%)**	**38 (59%)**	**0.02**
Peripheral involvement	30 (%)	54 (%)	0.17
bDMARD use			
Any time before pregnancy	16 (38%)	19 (30%)	0.49
Stop at + pregnancy test/1st trimester	8 (19%)	4 (6%)	0.09
Start/continue 1st trimester	7 (17%)	10 (16%)	0.89
Start in 2nd trimester	**5 (12%)**	**0**	**0.02**
Start in 3rd trimester	2 (5%)	0	0.30
Post-partum flare	11/34 (32%)	22/49 (45%)	0.36

Continuous variables were compared using Mann-Whitney test; categorical variables were compared using Chi-square with Yates' correction or Fisher's exact test.

Medications resumed to treat flare were steroids (29 pregnancies), csDMARDs (14 pregnancies) and TNF-inhibitors (7 pregnancies: 5 during the 2nd and 2 during the 3rd trimester).
A post-partum flare was registered in 33/83 (40%) of cases, without difference between 'flare' group vs 'without flare' group (Table 1), as well as between PsA vs 'other SpA' pregnancies (47% vs 33%, p=0.2).
Conclusion: In this cohort of SpA pregnancies, 40% experienced a flare during pregnancy and 40% during post-partum. Flares occurred more frequently in the 2nd trimester and especially in patients with axial involvement, requiring the start of a TNF-inhibitor during the 2nd or the 3rd trimester in 7 pregnancies. Having a flare during pregnancy was not associated with a post-partum flare.

Disclosure of Interests: None declared
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POS0152

DIRECT AND INDIRECT EFFECT OF TNF INHIBITORS ON SPINAL MOBILITY IN PEOPLE WITH AXIAL SPONDYLOARTHRITIS AND THE MEDIATOR ROLE OF DISEASE ACTIVITY

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Background: Although it may be difficult to detect changes in spinal mobility on the short term, spinal mobility is considered an important measure to assess the efficacy of drugs used to treat axial spondyloarthritis (axSpA). However, few studies evaluated the long-term impact of biologic treatment on spinal mobility.
Objectives: To describe the long-term effect of TNF inhibitors (TNFi) on spinal mobility in patients with axSpA, and to determine whether the use of TNFi treatment influences spinal mobility, and if this due to a direct or indirect effect (mediated by disease activity).
Methods: We performed a retrospective observational study, using data collected from patients with a clinical diagnosis of axSpA treated with TNFi at a tertiary care centre where disease activity and metrology assessments are routinely done. Adult patients with at least two Bath Ankylosing Spondylitis Metrology Index (BASMI) measurements were included. Disease activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score C-reactive protein (ASDAS). The longitudinal association between TNFi and improvement in BASDAI/ASDAS was tested using a linear mixed effects model with BASMI as dependent variable. To test whether TNFi had a direct effect on BASMI, not mediated by disease activity, we tested that TNFi treatment was not conditionally independent of BASMI given BASDAI/ASDAS (Figure 1). We tested whether the nodes TNFi and BASMI were disconnected if we removed BASDAI and ASDAS. To test this conditional independence, we first built a linear mixed effects model for BASMI given BASDAI or ASDAS when the patient was under TNFi and used this model to predict a 95% confidence interval (CI) for BASMI given the data for BASDAI/ASDAS when the patient was without TNFi. We checked whether the true value of BASMI lay within this 95% CI and performed a hypothesis test for binomial distribution where H0: p=0.95. To test for the indirect effect of TNFi on BASMI reduction, mediated through the disease activity, we regressed BASMI on BASDAI/ASDAS, TNFi (if there was a direct effect), demographics, presence of radiographic (r-) axSpA and HLA-B27 positivity, using a linear mixed effects model adjusted for within-patient correlation.

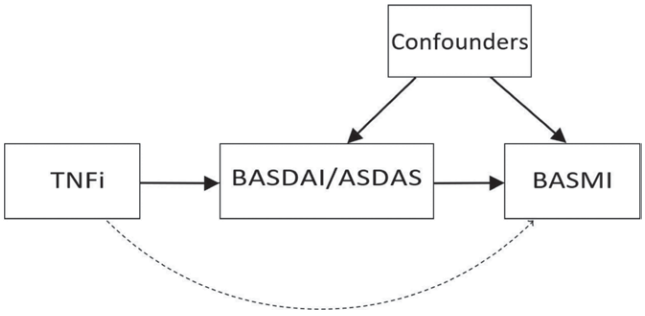

Figure 1. Indirect effect of TNFi on BASMI (represented by the full line), through the influence of TNFi on disease activity, adjusted by other confounders and direct effect of TNFi on BASMI (dashed line), independently of disease activity.

Results: Data from 188 patients and 1326 visits were analysed. Mean age was 45.6 (SD 11.6) years, mean disease duration was 15.8 (SD 9.64) years, 152 (80.9%) were male, 120 (73.6%) had r-axSpA, and 83 (74.8%) were HLA-B27 positive. Mean follow-up time was 8.0 (SD 4.4) years, ranging from 0.8 to 18.2 years. Treatment with TNFi was significantly associated with long-term improvement in BASMI (B=-0.423, 95% CI=[-0.553,-0.292], p<0.001). An indirect effect of TNFi on BASMI improvement was observed, mediated by reduction in disease activity, measured by BASDAI (B=0.146, 95% CI=[0.092, 0.200], p<0.001) or ASDAS (B=0.405, 95% CI=[0.260, 0.549], p<0.001). Using conditional independence tests, a direct effect of TNFi on BASMI improvement was also observed, independently of disease activity, when BASDAI was used (p<0.001) as a covariate, but not when ASDAS was used (p=0.3104). The direct effect of TNFi (B=-0.300, 95% CI=[-0.576,-0.025], p<0.001) on BASMI was estimated in the BASDAI-adjusted mixed effects model.