Autoimmunity Reviews 14 (2015) 376–386

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

State of the art: Reproduction and pregnancy in rheumatic diseases

Monika Østensen [a,*], Laura Andreoli [b], Antonio Brucato [c], Irene Cetin [d], Christina Chambers [e], Megan E.B. Clowse [f], Nathalie Costedoat-Chalumeau [g,h], Maurizio Cutolo [i], Radboud Dolhain [j], M.H. Fenstad [k], Frauke Förger [l], Marie Wahren-Herlenius [m], Guillermo Ruiz-Irastorza [n], Hege Koksvik [a], Catherine Nelson-Piercy [o], Yehuda Shoenfeld [p], Angela Tincani [q], Peter M. Villiger [r], Marianne Wallenius [s,t], Michael von Wolff [u]

[a] National Advisory Unit on Pregnancy and Rheumatic Diseases, Department of Rheumatology, St. Olavs Hospital, University Hospital of Trondheim, Norway
[b] Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Department of Clinical and Experimental Sciences, University of Brescia, Italy
[c] Department of Internal Medicine, Ospedale papa Giovanni XXIII Bergamo, Italy
[d] Department of Mother and Child, Hospital Luigi Sacco, University of Milano, Italy
[e] Department of Pediatrics, University of California San Diego, La Jolla, CA 92093-0828, USA
[f] Division of Rheumatology, Department of Medicine, Duke University Medical Center, Durham, NC, USA
[g] Université Paris-Descartes, Paris, France
[h] AP-HP, Hôpital Cochin, Centre de référence maladies auto-immunes et systémiques rares, Service de médecine interne, Paris, France
[i] Research Laboratories and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy
[j] Department of Rheumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[k] Department of Immunology and Transfusion Medicine, St. Olavs Hospital, Trondheim, Norway
[l] Department of Rheumatology and Clinical Immunology/Allergology, University Hospital of Bern, CH-3010 Bern, Switzerland
[m] Department of Medicine, Centre for Molecular Medicine, Karolinska Universitetssjukhuset, Stockholm, Sweden
[n] Autoimmune Diseases Research Unit, Department of Internal Medicine, Biocruces Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Bizkaia, Spain
[o] Women's Health Academic Centre, St Thomas' Hospital, London, UK
[p] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Aviv University, Tel-Hashomer, Israel
[q] Department of Rheumatology and Clinical Immunology, Ospedale Civile and University of Brescia, Brescia, Italy
[r] Department of Rheumatology and Clinical Immunology/Allergology, University Hospital of Bern, Bern, Switzerland
[s] National Service for Pregnancy and Rheumatic Diseases, Department of Rheumatology, Trondheim University Hospital, Trondheim, Norway
[t] Dept of Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[u] University Women's Hospital, Division of Gynaecological Endocrinology and Reproductive Medicine, University of Berne, Berne, Switzerland

ARTICLE INFO

Article history:
Received 12 December 2014
Accepted 23 December 2014
Available online 30 December 2014

Keywords:
Hormones
Fertility
Rheumatic Diseases
Pregnancy complications
Placenta
TNF inhibitors

ABSTRACT

Throughout the last decade, increasing awareness has been raised on issues related to reproduction in rheumatic diseases including basic research to clarify the important role of estrogens in the etiology and pathophysiology of immune/inflammatory diseases. Sub- or infertility is a heterogeneous condition that can be related to immunological mechanisms, to pregnancy loss, to disease burden, to therapy, and to choices in regard to family size. Progress in reproductive medicine has made it possible for more patients with rheumatic disease to have children. Active disease in women with rheumatoid arthritis (RA) affects their children's birth weight and may have long-term effects on their future health status. Pregnancy complications as preeclampsia and intrauterine growth restriction are still increased in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), however, biomarkers can monitor adverse events, and several new therapies may improve outcomes. Pregnancies in women with APS remain a challenge, and better therapies for the obstetric APS are needed. New prospective studies indicate improved outcomes for pregnancies in women with rare diseases like systemic sclerosis and vasculitis. TNF inhibitors hold promise for maintaining remission in rheumatological patients and may be continued at least in the first half of pregnancy. Pre-conceptional counseling and interdisciplinary management of pregnancies are essential for ensuring optimal pregnancy outcomes.

Contents

* Corresponding author.
E-mail address: monika.ostensen@gmail.com (M. Østensen).

http://dx.doi.org/10.1016/j.autrev.2014.12.011
1568-9972/

1. Introduction

Throughout the last decade, increasing awareness has been raised on issues related to reproduction in chronic diseases. Rheumatic diseases can affect quality of life and reproduction in both genders. Hormones, fertility, pregnancy, and management of high-risk pregnancy are important topics for patients and their doctors alike. This article gives a concise overview of current basic and clinical research presented at the VIII International Conference on Reproduction and Pregnancy and the rheumatic diseases 25–27, 2014 September in Trondheim, Norway.

2. Sex hormones and autoimmune diseases

The preponderance of women affected by chronic immune/inflammatory diseases clearly indicates that female sex hormones play an important role in the etiology and pathophysiology of autoimmunity [1]. In human subjects estrogens are generally considered as at least enhancing the humoral immune response. They act on cells by their peripheral metabolites rather than through their serum levels that may exert opposite dose-related effects [2].

Estrogen receptors (ERα and ERβ) are necessary for the action of estrogens. Recently, anti-ERα antibodies were detected in 45% of patients with systemic lupus erythematosus (SLE), whereas anti-ERβ antibodies were undetectable [3]. In healthy donors, anti-ERα antibodies induced cell activation and consequent apoptotic cell death in resting lymphocytes. At the same time, they induced proliferation of anti-CD3-stimulated T lymphocytes, a mechanism that might contribute to autoreactive T cell expansion. A significant association between anti-ERα antibody levels and clinical parameters, like the SLE Disease Activity Index (SLEDAI) and arthritis, was found [3].

Several investigations support an accelerated aromatase-mediated peripheral metabolic conversion of upstream androgen precursors to estrogen metabolites in peripheral tissues affected by immune/inflammatory reactions, both in male and female patients [4]. In synovial tissue from rheumatoid arthritis (RA) patients, altered peripheral sex hormone synthesis (intracrine, e.g., at the level of macrophages and fibroblasts) mainly results in stimulation of cell proliferation and cytokine production (i.e. TNF) by these metabolites. It was shown that RA synovial cells mainly produce the cell proliferation promoting 16alpha-hydroxyestrone which, in addition to 16alpha-hydroxy-17beta-estradiol, is the downstream estrogen metabolite that interferes with monocyte proliferation [5]. Therefore, a preponderance of 16alpha-hydroxylated estrogens is an unfavorable sign, at least, in synovial inflammation and possibly related synovial tissue hyperplasia. Interestingly, urinary concentration and total urinary loss of 2-hydroxyestrogens was found 10 times higher in healthy subjects compared to RA or SLE patients irrespective of prior prednisolone treatment or sex [2]. The intracrine synthesis of active estrogen metabolites at the level of cells involved in the immune response represents a common pathway that characterizes a similar final immune reactivity in both male and female patients [4].

2.1. Contraception

Traditionally, exogenous estrogens were considered to have the potential of worsening autoimmune processes. Typical oral contraceptive pills contain both estrogen and progesterone (combined oral contraceptives). Two randomized trials of these pills in women with mild-moderate stable SLE found no increase in SLE activity [6]. However, women with very active SLE or active lupus nephritis were not included in these trials [6]. The risk of thrombosis remains a significant concern, and estrogens should be avoided in women with antiphospolipid syndrome (APS), high levels of antiphospholipid antibodies (aPL), nephrotic-range proteinuria, or other conditions that increase thrombotic risk. The relative risk of venous thrombosis for combined oral contraceptives with 30–35 μg ethinylestradiol and gestodene, desogestrel, cyproterone acetate or drospirenone (3rd or 4th generation progestogens) is similar and about 50–80% higher than for combined oral contraceptives with levonorgestrel (2nd generation progestogen) [7].

3. Fertility

Fertility problems in women with rheumatic disease occur not only in diseases with extensive systemic inflammation and autoantibody production, but also in the predominantly inflammatory joint diseases (IJD) [8]. Women with IJD have a prolonged time to pregnancy compared to women in the general population, and seem also to require assisted reproduction more often [9]. Whether they also have a reduced ovarian reserve has not been clarified. In a prospective study of 245 women with rheumatoid arthritis desiring children, 42% experienced a greater than 12 month interval until conception [10]. Disease activity and therapy were found associated with a prolonged interval to achieve pregnancy.

Women with rheumatic disease have fewer children than age matched controls from the general population [11]. A reduced family size can be caused by increased pregnancy losses as well as disease related choices. Age at the time of diagnosis is of importance for parity/nulliparity and for the final number of children. Women diagnosed with IJD before 25 years of age are more often childless or have fewer children than women diagnosed after 25 years of age [8]. Studies have also shown that women with IJD are older than age matched controls at their first delivery and thus have a shorter reproductive period.

The rate of early and late pregnancy losses is significantly increased in the APS, particularly when combined with SLE. Danowski et al. 2009