Contraception and Pregnancy in Patients with Rheumatic Disease

Lisa R. Sammaritano
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Editors
Lisa R. Sammaritano
Division of Rheumatology
Hospital for Special Surgery
Weill Cornell Medical College
New York, NY, USA

Bonnie L. Bermas
Division of Rheumatology
Brigham and Women's Hospital
Harvard Medical School
Boston, MA, USA

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To our patients, who make going
to work a pleasure;
To our families, who make coming
home a joy.

Lisa R. Sammaritano
Bonnie L. Bermas

Preface

Rheumatologic diseases disproportionally impact women during their reproductive years. Rheumatologists are not trained as obstetricians and many of us lack the experience of managing pregnant patients. Similarly, most obstetricians are not familiar with the intricacies of treating rheumatologic disorders. Thus, clinicians are often faced with difficult management issues that surround family planning including contraception, assisted reproductive technologies, pregnancy, and nursing.

The various rheumatologic disorders impact pregnancy outcomes differently. Some diseases such as systemic lupus erythematosus (SLE) can increase the risk of pregnancy complications. Others such as rheumatoid arthritis (RA) are less likely to do so. In turn, pregnancy itself induces immunologic changes that can either cause symptoms to improve or worsen. Competing needs of the developing fetus and the mother may limit medications typically used in disease management, compounding the challenge of disease management. Additionally, the type of contraception and method of assisted reproductive technology may need to be adjusted in women with rheumatologic disorders.

In creating this textbook, our hope was to provide information and guidance to clinicians in the area of reproduction and rheumatic disorders. What follows summarizes the current state of knowledge in this area. This textbook starts by reviewing the immunology and obstetric management of pregnancy in general. It then provides general guidelines for pre-pregnancy assessment of the rheumatology patient. In Part II, pregnancy in specific rheumatologic disorders is discussed, including SLE, Sjogren's syndrome, mixed connective tissue disease, undifferentiated connective tissue disease, antiphospholipid syndrome, RA and seronegative spondyloarthropathy, systemic sclerosis, vasculitides, and inflammatory myositis. In Part III, contraception and assisted reproductive technology methods are reviewed. Finally, the topics of neonatal lupus, medication use during pregnancy and lactation, and the long-term outcome of children of rheumatic disease patients are covered.

As rheumatologists who have been interested in this field for many years, we have faced many challenges of family planning in our patients with rheumatologic disorders. Along with these challenges have come incredibly gratifying experiences in negotiating contraception and pregnancy alongside these patients. We are grateful to them for letting us participate in these journeys. We are also indebted to our coauthors, each of whom provided invaluable expertise in an important area in this field.

New York, NY, USA — Lisa R. Sammaritano
Boston, MA, USA — Bonnie L. Bermas

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Contributors

Laura Andreoli Rheumatology and Clinical Immunology, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Brescia, Italy

Bonnie L. Bermas Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

D. Ware Branch Department of Obstetrics and Gynecology, University of Utah Health Sciences Center and Intermountain Health Care, Salt Lake City, UT, USA

Jill P. Buyon Department of Rheumatology, New York University School of Medicine, New York, NY, USA

Kenneth I. Cadesky Department of Obstetrics and Gynecology (Reproductive Endocrinology and Infertility), Mount Sinai Hospital; LifeQuest Centre for Reproductive Medicine, Toronto, ON, Canada

Christine A. Clark LifeQuest Centre for Reproductive Medicine, Toronto, ON, Canada

Cecily A. Clark-Ganheart Department of Obstetrics & Gynecology, Division of Maternal-Fetal Medicine, Medstar Washington Hospital Center, Medstar Georgetown University Hospital, Washington, DC, USA

Megan E.B. Clowse Division of Rheumatology and Immunology, Duke University Hospital, Durham, NC, USA

Stephen J. Di Martino Division of Rheumatology, Hospital for Special Surgery, New York, NY, USA

Elisa Fazzi Unit of Child and Adolescent Neuropsychiatry, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Brescia, Italy

Alessandro Iodice Unit of Child and Adolescent Neuropsychiatry, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Brescia, Italy

Peter M. Izmirly Department of Rheumatology, New York University School of Medicine, New York, NY, USA

Lindsay Lally Division of Rheumatology, Hospital for Special Surgery, New York, NY, USA

Carl A. Laskin Departments of Medicine (Rheumatology) and Obstetrics & Gynecology, (Reproductive Endocrinology and Infertility), LifeQuest Centre for Reproductive Medicine, University of Toronto, Toronto, ON, Canada

Alana B. Levine Division of Rheumatology, Hospital for Special Surgery, New York, NY, USA

Michael D. Lockshin Division of Rheumatology, Hospital for Special Surgery, New York, NY, USA

Andrea Lojacono Obstetrics and Gynecology, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Brescia, Italy

Antonella Meini Unit of Pediatric Immunology and Rheumatology, Pediatric Clinic, Spedali Civili and University of Brescia, Brescia, Italy

Barbara Mendez Albert Einstein College of Medicine, Department of Rheumatology, Montefiore Medical Specialists, Scarsdale, NY, USA

Mario Motta Neonatology and NICU, Spedali Civili and University of Brescia, Brescia, Italy

Cecilia Nalli Rheumatology and Clinical Immunology, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Brescia, Italy

Monika Østensen Department of Rheumatology, National Service for Pregnancy and Rheumatic Disease, University Hospital of Trondheim, Trondheim, Norway

Rossella Reggia Rheumatology and Clinical Immunology, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Brescia, Italy

Lisa R. Sammaritano Division of Rheumatology, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, USA

Amit Saxena NYU Langone Medical Center, Center for Musculoskeletal Care, New York, NY, USA

Danny J. Schust Department of Obstetrics, Gynecology and Women's Health, University of Missouri, Columbia, MO, USA

Robert F. Spiera Division of Rheumatology, Hospital for Special Surgery, New York, NY, USA

Karen A. Spitzer LifeQuest Centre for Reproductive Medicine, Toronto, ON, Canada

Virginia D. Steen Department of Medicine/Rheumatology, Medstar Georgetown University Hospital, Washington, DC, USA

Amanda J. Stephens Department of Obstetrics, Gynecology and Women's Health, University of Missouri, Columbia, MO, USA

Julia Timofeev Department of Obstetrics & Gynecology, Division of Maternal-Fetal Medicine, Medstar Washington Hospital Center, Medstar Georgetown University Hospital, Washington, DC, USA

Angela Tincani Rheumatology and Clinical Immunology, Department of Clinical and Experimental Sciences, Spedali Civili and University of Brescia, Brescia, Italy

Marianne Wallenius Department of Rheumatology, National Service for Pregnancy and Rheumatic Disease, University Hospital of Trondheim, Trondheim, Norway

Institute of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

Sara Wasserman Division of Rheumatology and Immunology, Duke University Hospital, Durham, NC, USA

Luchin F. Wong Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City, UT, USA

Part I
Basics of Pregnancy

Chapter 1
Immunology of Pregnancy

Danny J. Schust and Amanda J. Stephens

Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
ANG2	Angiopoietin 2
CMV	Cytomegalovirus
CSA	Chondroitin sulfate A
CTL	Cytotoxic T lymphocyte
DAF	Decay-accelerating factor
DC	Dendritic cell
EVT	Extravillous cytotrophoblast
hCG	Human chorionic gonadotropin
HLA	Human leukocyte antigen
IFN	Interferon
IL	Interleukin
KAR	Killer activation receptor
KIRS	Killer immunoglobulin-like receptors
LIF	Leukemia inhibitory factor
LIRS	Leukocyte immunoglobulin-like receptors
MAC	Membrane attack complex
MBL	Mannose-binding lectin
MCP	Membrane cofactor protein
MHC	Major histocompatibility complex
MS	Multiple sclerosis
NF-κB	Nuclear factor-kappa B

D.J. Schust, M.D. (✉) • A.J. Stephens, M.D.
Department of Obstetrics, Gynecology and Women's Health, University of Missouri,
500 North Keene Street, Suite 203, Columbia, MO 65203, USA
e-mail: SchustD@health.missouri.edu

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NK	Natural killer
PIBF	Progesterone-induced binding factor
PIGF	Placental growth factor
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
SynT	Syncytiotrophoblast
TCR	T cell receptor
Tfh	Follicular helper T lymphocyte
TGF	Transforming growth factor
Th	T helper
TNF	Tumor necrosis factor
Treg	T regulatory lymphocyte
UL	Unique long
uNK	Uterine natural killer lymphocyte
US	Unique short
VEGFC	Vascular endothelial growth factor C
VZV	Varicella zoster virus

Introduction

Through numerous pathways, the immune system works to protect an individual from exogenous pathogens and from neoplastic cellular changes. During development, immune cells are programmed to discriminate self from non-self and to respond appropriately at initial encounters with self and foreign antigens. When this recognition mechanism fails, the immune system may react inappropriately against self antigens and initiate a series of events that result in autoimmune disorders. During pregnancy, alterations of these recognition processes by the maternal immune system determine the success or failure of continued fetal growth and development until birth. Pregnancy presents a particular immunologic challenge because the tissue antigens presented to the maternal immune system are a combination of self (maternally derived) and non-self (paternally derived) constituents.

The Menstrual and Reproductive Cycle

Throughout the menstrual cycle and pregnancy, changes occur within the lining of the uterine cavity (endometrium) in response to reproductive hormones, particularly the reproductive steroids, estrogen and progesterone [1]. The proliferative phase of the menstrual cycle is characterized by estrogen dominant regeneration of the endometrium [2]. After initial "healing," regrowth of the ever-changing endometrial "functionalis" layer begins approximately 5 days after the beginning of the menstrual cycle, which is defined clinically as day 1 of bright red vaginal bleeding.

This regrowth results from rapid proliferation of the endometrial glands and stroma, which gives this phase of the menstrual cycle its common name—the proliferative phase. Important to this regrowth is a revascularization of the endometrium, which was poorly vascularized during the relatively hypoxic "sloughing" phase of menstruation. Alterations in the length of the proliferative phase are largely responsible for variations from the classical 28 day menstrual cycle. Near the end of the proliferative phase, endocrine, autocrine, and paracrine events within the hypothalamic–pituitary–ovarian axis cause a rapid increase or surge in luteinizing hormone (LH) secretion and ovulation occurs soon thereafter. During this time, local and systemic progesterone levels begin to increase while estrogen levels decrease somewhat. If implantation follows, progesterone levels continue to rise. This progesterone dominant part of the menstrual cycle is called the luteal phase and its length is fairly consistent from cycle to cycle. The endometrium of the luteal phase responds to this new hormonal milieu by undergoing a transformation in preparation for implantation that is called decidualization. The endometrium is now renamed the decidua. Between cycle days 20–24, specific morphologic changes in the decidua characterize the "window of implantation," including decreased microvilli and the development of cilia with luminal protrusions on the apical glandular surface called pinopodes [3]. The maternal uterine spiral arteries develop and continue to grow. The dominant follicle that released the oocyte at the time of ovulation develops into the corpus luteum which produces progesterone to maintain an early pregnancy until the placenta is capable of sufficient progesterone production, approximately 7–9 weeks of gestation. If implantation does not occur, the corpus luteum regresses in a predictable fashion. In response to falling levels of estrogen and progesterone, a series of cytokine-, chemokine-, and prostaglandin-mediated events lead to endometrial hypoxia, endometrial shedding, and menstruation. If implantation occurs and the pregnancy progresses normally, estrogen, progesterone, human chorionic gonadotropin (hCG), and a variety of other hormones continue to increase to support the developing embryo.

Implantation is one of the most complex and important events of pregnancy and continues to be targeted in many investigations of pregnancy immunology. At least 50 % of all pregnancies fail to synchronize the necessary events of implantation and only 25 % of all fertilized ova will generate a live birth. The majority of early pregnancy losses are of chromosomally abnormal human embryos [4–6]. Major histocompatibility antigens that have the potential to induce an alloimmune response in the maternal host are expressed on the surfaces of human preimplantation embryos but the role of these antigens in pregnancy has not been fully elucidated (described in detail below) [7]. While it is generally accepted that the mother recognizes and responds to these alloantigens, it is possible that aberrant maternal recognition of these antigens in certain pregnancies may play a role in implantation failure [8].

Approximately 6 days after fertilization in the fallopian tube, the developing embryo becomes a blastocyst that has an inner cell mass that will develop into the fetus and an outer trophectoderm layer, which will subsequently differentiate to become the multilayered placenta. Once the blastocyst attaches to the decidua, the trophectoderm differentiates into the syncytiotrophoblast and

cytotrophoblast. Initially, the syncytiotrophoblast invades into the decidua and allows the blastocyst to be enveloped with maternal tissue. The trophoblast quickly perforates the maternal capillaries and the spaces within the syncytium are filled with maternal blood. These areas enlarge and fuse to become the intervillous space of the human placenta, the site at which nutrient and gas exchange occurs between the mother and her developing embryo. Two weeks after implantation, the cytotrophoblast cell subpopulation in the placenta proliferates into buds that grow through the syncytium. The trophoblast cells of the post-implantation placenta are generally divided into two populations: (1) villous trophoblast that covers the chorionic villi and interacts with maternal blood in the intervillous space and (2) extravillous trophoblast (EVT) that migrate into the decidua and surround the maternal spiral arteries, destroying the muscular walls and leading to endothelial cell swelling. Like syncytiotrophoblast, EVT come into direct contact with maternal peripheral blood (Fig. 1.1) [9]. Remodeling of the maternal spiral arteries by endovascular trophoblast creates low resistance vascular channels that are largely unable to respond to maternal vasoactive stimuli; this prevents compromise of the uteroplacental blood flow during maternal stressors. The remaining extravillous cytotrophoblast cells will be in direct contact with the immune cells of the maternal decidua. EVT typically invade through the decidua and invasion can extend as far as the inner third of the myometrium in healthy pregnancies. Alterations in the depth of such invasion have been seen in pregnancy pathologies such as preeclampsia and intrauterine growth restriction (poor invasion) and placenta percreta (overly robust invasion).

Basic Principles of Immune Response

The immune system is divided into two general methods of response, the innate immune response and the acquired immune response. Cooperation between these two systems is often needed to provide effective responses to a foreign pathogen as these responses differ in intensity, onset, and specificity.

Innate Immunity

When a foreign pathogen enters the body, the innate immune mediators are the first to encounter the pathogen. The innate immune response is comprised of a variety of cells and tissues that provide initial host defense. Epithelial tissues containing protective tight intercellular junctions, such as those in the skin and mucosal membranes, are often the first location of pathogen exposure. Other components of the innate immune response include phagocytic and cytotoxic cells and a range of

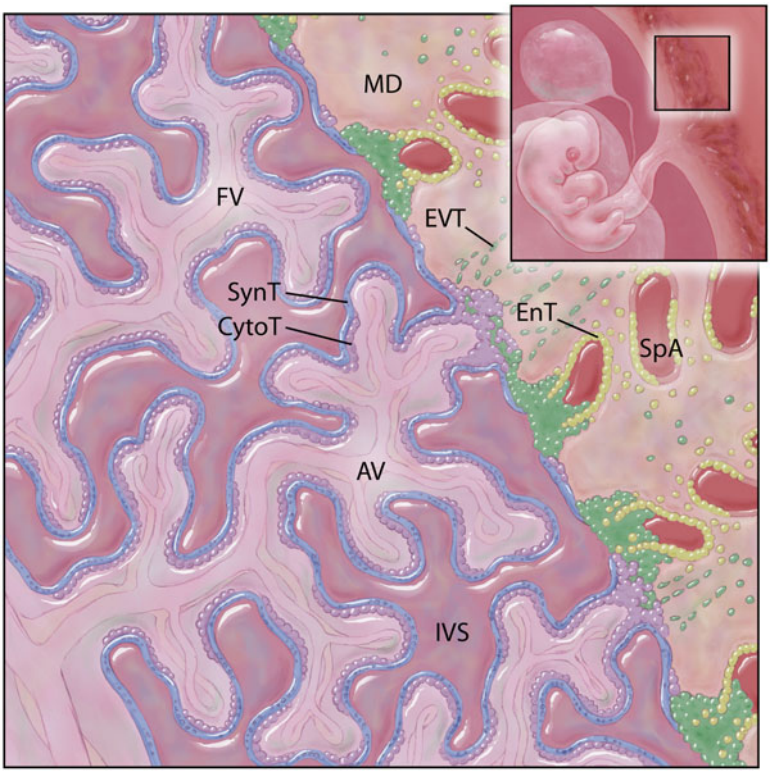

Fig. 1.1 The human maternal–fetal interface in early pregnancy. The fetal aspect of the maternal–fetal interface is comprised of a very large number of branching placental villi that are bathed by the maternal blood filling the intervillous space (IVS). Placental villi contain fetal vessels (FV) embedded in stroma and covered by trophoblast. Floating villi (FV) and anchoring villi (AV) are covered by a mostly continuous (in early pregnancy) layer of syncytiotrophoblast, the multinucleated syncytium of cells that coats the IVS and comes into direct contact with maternal blood. Syncytiotrophoblast is the product of fusion of the underlying cytotrophoblast progenitor cells. Unlike floating villi, which float freely in the IVS, anchoring villi cross the IVS and attach to the maternal decidua (MD). At the tips of the anchoring villi, some cytotrophoblast cells cease proliferating and transform into invasive extravillous cytotrophoblast (EVT) cells. These cells leave the anchoring villi to invade through the decidua, often reaching as far as the inner third of the uterine myometrium. A subset of extravillous cytotrophoblast cells, called endovascular trophoblast (EnT) remodels the maternal uterine spiral arteries (SpA), replacing cells of the maternal vascular wall and creating a vaso-inert conduit for the maternal blood that dumps into the IVS after about 11–12 weeks of gestation. From soon after initial implantation until about 10–11 weeks of gestation, extravillous trophoblast plugs the ends of the SpA and the IVS is filled with nutrient rich exudates

effector molecules, including inflammatory response molecules, antimicrobial peptides, and cytokines. The innate immune response is a rapid generalized response that is not specific to the pathogen or other foreign antigen. It is unable to establish memory toward a pathogen or other foreign antigen and therefore cannot develop adaptations to the antigen that promote more rapid or robust immunologic responses upon future exposure.