WAYNE DAY 2019
HONORING

JACK D. SOBEL, MD – DEAN, SCHOOL OF MEDICINE
KAMRAN S. MOGHISSI, MD

INFECTIOUS DISEASES IN PREGNANCY

DECEMBER 7-8, 2019

SHINOLA HOTEL
DETROIT, MICHIGAN

http://obgyn.med.wayne.edu/wayne-day
Wayne State University School of Medicine
Department of Obstetrics and Gynecology

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Wayne State University
School of Medicine Alumni Affairs
On behalf of the Wayne Day planning committee, and the Department of Obstetrics and Gynecology, I am honored and delighted to welcome you to the 38th Annual Wayne Day Symposium on Infectious Diseases in Pregnancy in Detroit, Michigan. I believe we have created a successful platform for national and international speakers to share their research in infectious diseases and women’s health.

We have an exciting program this weekend that includes: three keynote speakers: the Distinguished Dean’s lectureship presented by Michal A. Elovitz, MD, of the University of Pennsylvania, Perelman School of Medicine; the Kamran S. Moghissi, MD lectureship presented by Errol R. Norwitz, MD, PhD, MBA, of Tufts University School of Medicine; and the Keynote Address presented by David A. Eschenbach, MD of the University of Washington School of Medicine.

As the conference coordinator of Wayne Day 2019: Infectious Diseases in Pregnancy, I recognize that the success of the conference depends ultimately on the diligent staff who have worked continuously with us in planning and organizing both the program and supporting social arrangements. In particular, I thank the program co-directors: Drs. Kevin Theis and Lami Yeo, for their advice and superb recommendations, and our exhibitors for their continued financial support.

Lastly, I would also like to thank all the conference participants, who are the foundation of this event. I hope you enjoy this year’s event and invite you to take a moment this weekend to experience Detroit during the holiday season.

Chaur-Dong Hsu, MD, MPH
Chair, Department of Obstetrics and Gynecology
Wayne State University School of Medicine

Kevin R. Theis, PhD
Co-Activity Director

Lami Yeo, MD
Co-Activity Director

December 7-8, 2019
Shinola Hotel Detroit, MI
Jack D. Sobel, M.D. - Dr. Sobel is Dean of the School of Medicine at Wayne State University, previously Chair of Internal Medicine and served as Chief of Division of Infectious Diseases and Distinguished Professor of Medicine at Wayne State University School of Medicine. A graduate of the University of Witwatersrand, Johannesburg, South Africa. Dr. Sobel did his fellowship in Infectious Diseases at the National Institute of Health, Bethesda, Maryland and the Medical College of Pennsylvania. He is a board certified internal medicine specialist in the United States, the United Kingdom, Israel and South Africa and became a Master in the American College of Medicine in 2013.

He has specialized as a “Candidologist”, specifically in Candida infection of the genitourinary tract. His research interests have encompassed microbiology, immunology and molecular biology of Candida infections including immunologic studies as well as tissue culture methods and development of animal models of experimental vaginal candidiasis.

Accordingly, after more than a decade of studying systemic candidiasis and candidemia, Dr. Sobel chose to limit his mycology interest to clinical vulvovaginal candidiasis seeing and studying women with refractory and recurrent vaginal candidiasis. In particular, he has been the first to describe and report multi-drug resistant vaginitis due to a variety of Candida species as well as developing new treatment protocols. His focus on these infections in women has contributed to progress in unravelling the genetic basis for these infections. Over the last decade, he has turned his attention to other vaginal inflammatory conditions, notably recurrent and refractory bacterial vaginosis and immune mediated auto-inflammatory vaginitis focusing on the role of the vaginal microbiome in the pathogenesis of vaginal diseases. His ground-breaking treatments are the standard of care throughout the world and millions of women have benefitted from his innovative therapeutic regimens.

He is the author of more than 500 peer-reviewed scholarly manuscripts, has authored several books, and contributed more than 150 book chapters. In viewing his career contributions while Chief of Infectious Diseases at Wayne, more than 70 ID fellows graduated as a specialists. In the eyes of these graduates, Dr. Sobel is remembered for his commitment to clinical excellence, specializing in diagnostic challenges and therapeutic innovation. As a role model, he was demanding in encouraging intellectual medical curiosity and his graduates were known as the “why” doctors.

Serving as Dean of the largest medical school in North America for the last 5 years has not diminished his passion or commitment to infectious diseases involving the lower genital tract of women, and challenging the task of educating medical students in the modern era.

The Department of Obstetrics and Gynecology honors Dean Sobel at this year’s Wayne Day 2019: Infectious Diseases in Pregnancy, with the Distinguished Dean’s Lectureship presented by Michal A. Elovitz, MD of the University of Pennsylvania, Perelman School of Medicine.
Kamran S. Moghissi, M.D., is professor emeritus of obstetrics and gynecology for the Wayne State University School of Medicine. He joined the faculty in 1962.

The author and coauthor of more than 360 publications in scientific journals and editor or co-editor of 17 books, he has served as president of the American Society for Reproductive Medicine (1990-91), the Society of Reproductive Endocrinologist (1989-90) and as the first president of the Michigan Society of Reproductive Endocrinologists. He has also served as a member of the U.S. Food and Drug Administration's Fertility and Maternal Health Drug Advisory Committee as a member and chair of the Reproductive Endocrinology Study Section of the National Institutes for Health, as a member of the Population Research Committee of the National Institute of Child Health and Human Development, and a consultant to the World Health Organization. He has been the recipient of numerous research grants from the National Institutes of Health, the WHO and pharmaceutical companies.

The recipient of the National Presidents Award of the Michigan State Medical Society and the Wayne County Medical Society's Professional Achievement Award, Dr. Moghissi established the first Comprehensive Infertility Clinic at Wayne State University/Hutzel Hospital and the first successful In Vitro Fertilization program in Michigan. He has served as chief of the Department of Obstetrics and Gynecology at Harper-Grace Hospital and Hutzel Hospital and as chair of the Department of Obstetrics and Gynecology at Wayne State University and the Detroit Medical Center. His other honors include an honorary professorship at Zhejiang Chinese Medical University, the Pathfinders in Medicine Award, the Weiner Recognition Award and the Distinguished Service Award from Wayne State University.

In 1963, Grand Rounds was organized by Dr. Moghissi as an informal meeting between the WSU Department of Obstetrics and Gynecology residents and attendings. As Director, Dr. Moghissi invited OB/GYN attendings and residents from various hospitals within the Tri-County area to attend. Subsequently, this invitation lead to all the hospitals combining their OB/GYN rounds with WSU. Eventually, each surrounding hospital within the Tri-County area that participated with WSU began to organize a grand rounds program within their respective institutions.

In 1965, the American College of Obstetrics and Gynecology of Michigan organized and assigned Wayne Day to Wayne State University, which was to be held the first Tuesday of the month in December. In 1981, the WSU Department of Obstetrics and Gynecology petitioned to change Wayne Day to the Kamran S. Moghissi, MD Day in recognition of Dr. Moghissi's hard work and dedication to the department. An annual lectureship in his name in the WSU Department of Obstetrics and Gynecology was established.

In 1997, Wayne State University honored Dr. Moghissi by establishing the Kamran S. Moghissi, M.D., Chair in Reproductive Endocrinology & Infertility.
Target Audience

Obstetricians & Gynecologists, Internal Medicine, Family Medicine, Pediatrics, and Biochemistry Microbiology and Immunology (BMI) Physicians, Fellows, Residents, Nurses, and other Allied Health Professionals

Educational Objectives

At the end of this program the participant will be able to:

- Develop an understanding of the current state of knowledge and tools on how variation in the human microbiome, and especially the cervical, vaginal and urinary microbiomes, translates to disease.
- Understand the pathogenesis, diagnosis and the new treatment of intra-amniotic infection and inflammation.
- Gain an improved understanding of bacterial and viral infections in pregnancy, including pathophysiology, management, and treatment.
- Develop a strategic bundle in the reduction of Cesarean section surgical site infection.
- Understand and update an obstetric sepsis protocol.
- Understand the effectiveness of vaccination in the prevention of infectious disease in pregnancy.

Continuing Medical Education Credit

The Wayne State University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Wayne State University School of Medicine designates this live activity for a maximum of 15.00 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ACOG Cognate

The American College of Obstetrics and Gynecologists has assigned 15 cognate credits (Formal Learning) to this program.
Commercial Relationship Disclosure:

Wayne State University School of Medicine Office of Continuing Medical Education endorses the Standards of the Accreditation Council for Continuing Medical Education and the Guidelines of the American Medical Association.

Wayne State University School of Medicine requires that all presentations at CME activities be fair, balanced free of commercial bias, and fully supported by scientific evidence.

Everyone who is in a position to control the content of a continuing medical education activity is required to disclose relevant relationships with commercial companies whose products or services are discussed in educational presentations. The ACCME considers relationships of the person involved in the CME activity to include financial relationships of a spouse or partner.

Disclosure of a relationship is not intended to suggest bias in any presentation but is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

All potential conflicts of interest have been resolved prior to this program.

Acknowledging a relevant relationship with the following companies or organizations having a direct interest in the subject of this presentation includes:

David M. Aronoff, MD
   **Commercial relationships:** Consulting Fees: (e.g. advisory boards), Honoraria: NAEJA-RGM, BLC, ABEL, Synthetic Biologics, Cepheid, Sanofi. Grant/ Research Support (Principal Investigator): NIH, March of Dimes, Pfizer

Suresh B. Boppana, MD
   **Commercial relationships:** Consulting Fees: (e.g. advisory boards), Honoraria: CMV Vaccine Advisory Committees – Merck & Sanofi

Gregory A. Buck, PhD
   **Commercial relationships:** None

Michal A. Elovitz, MD
   **Commercial relationships:** None

David A. Eschenbach, MD
   **Commercial relationships:** None

Bernard Gonik, MD
   **Commercial relationships:** None

Chaur-Dong Hsu, MD, MPH
   **Commercial relationships:** None

Muhammad Jaffer, MD
   **Commercial relationships:** None

Karen E. Johnson, MD
   **Commercial relationships:** Royalty, Receipt of Intellectual Property Rights / Patient Holder: UpToDate/Wolters Kluwer Health Employee: Self
Theodore B. Jones, MD  
**Commercial relationships**: None

Marian Kacerovsky, MD, PhD  
**Commercial relationships**: None

Amanda L. Lewis, PhD  
**Commercial relationships**: Grant/Research Support (Principal Investigator): Metrodora Therapeutics. Employee: Self

David A. Maclntyre, PhD  
**Commercial relationships**: None

Elizabeth J. May, MD, PhD  
**Commercial relationships**: None

Gil G. Mor, MD, PhD  
**Commercial relationships**: None

Indira U. Mysorekar, PhD  
**Commercial relationships**: None

Errol R. Norwitz, MD, PhD, MBA  
**Commercial relationships**: Consulting Fees: (e.g. advisory boards), Honoraria Illumina, Natera, Hologic, Ferring, and SenaCare Royalty, Receipt of Intellectual Property Rights/Patient Holder: Bayer Pharmaceuticals Grant/Research Support: Illumina

Roberto Romero, MD, DMed, Sci  
**Commercial relationships**: None

Thomas M. Schmidt, PhD  
**Commercial relationships**: None

Carlos Simón, MD, PhD  
**Commercial relationships**: Consulting Fees: (e.g. advisory boards), Honoraria: Igenomix SL, Ferring, Therannex, Serono Royalty, Receipt of Intellectual Property Rights / Patent Holder: Igenomix SL, Ferring Employees: Spouse or Partner: Igenomix SL

Jack D. Sobel, MD  
**Commercial relationships**: Grant/Research Support (Principal Investigator): Scynexis Comp, and Mycovia

Kevin R. Theis, PhD  
**Commercial relationships**: None

Lami Yeo, MD  
**Commercial relationships**: None
## SATURDAY, DECEMBER 7, 2019

### PROGRAM AGENDA

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:00 am</td>
<td>Registration &amp; Continental Breakfast</td>
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<tr>
<td>7:20 am</td>
<td>Welcome / Opening Remarks</td>
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<tr>
<td></td>
<td>Lami Yeo, MD</td>
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<td><strong>MODERATOR: Kevin R. Theis, PhD</strong></td>
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### MICROBIOME, PREGNANCY, AND PRETERM BIRTH

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:30 am</td>
<td>The Study and Management of the Human Microbiome</td>
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<tr>
<td></td>
<td>Thomas M. Schmidt, PhD</td>
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<tr>
<td>8:10 am</td>
<td><strong>DISTINGUISHED DEAN’S LECTURE</strong></td>
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<tr>
<td></td>
<td>Cervicovaginal Microbiome and Preterm Birth</td>
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<tr>
<td></td>
<td>Michal A. Elovitz, MD</td>
</tr>
<tr>
<td>8:50 am</td>
<td>Vaginal Microbiome in Pregnancy and Preterm Birth</td>
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<tr>
<td></td>
<td>Gregory A. Buck, PhD</td>
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<tr>
<td>9:30 am</td>
<td>Assessment of Vaginal Microbiota-Host Interactions in Preterm Birth</td>
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<td></td>
<td>David A. MacIntyre, PhD</td>
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**BREAK WITH EXHIBITORS**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>10:30 am</td>
<td>Is There a Placental Microbiota?</td>
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<tr>
<td></td>
<td>Kevin R. Theis, PhD</td>
</tr>
<tr>
<td>11:10 am</td>
<td>Ralstonia Insidiosa: A Black Swan at the Maternal Fetal Interface?</td>
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<tr>
<td></td>
<td>Indira U. Mysorekar, PhD</td>
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<tr>
<td>11:50 am</td>
<td>The Endometrial Microbiota and Its Importance in Reproductive Success</td>
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<td></td>
<td>Carlos Simón, MD, PhD</td>
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**LUNCH WITH EXHIBITORS**

<table>
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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>12:30 pm – 1:30 pm</td>
<td>LUNCH WITH EXHIBITORS</td>
</tr>
</tbody>
</table>
## Saturday, December 7, 2019

**Program Agenda Continues**

**Moderator:** Kevin R. Theis, PhD

### Intra-amniotic Infection / Inflammation

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>1:30 pm</td>
<td>Intra-Amniotic Inflammation and Infection: Clinical Diagnosis and Significance</td>
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<tr>
<td></td>
<td>Marian Kacerovsky, MD, PhD</td>
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<tr>
<td>2:10 pm</td>
<td>Treatment of Intra-Amniotic Infection in Preterm Labor, Cervical Insufficiency and Preterm PROM</td>
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<tr>
<td></td>
<td>Roberto Romero, MD, DMed, Sci</td>
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<tr>
<td>2:50 pm–3:05 pm</td>
<td><strong>Afternoon Break</strong></td>
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### Bacterial Infection in Pregnancy

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>3:05 pm</td>
<td>Infectious Vaginitis in Pregnancy</td>
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<td></td>
<td>Jack D. Sobel, MD</td>
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<tr>
<td>3:45 pm</td>
<td>The Vaginal Microbiome and Group B Streptococcal Pathogenesis: Insights from a Mouse Model</td>
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<td></td>
<td>Amanda L. Lewis, PhD</td>
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<tr>
<td>4:25 pm</td>
<td>Group B Streptococcus Infection in Pregnancy</td>
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<td></td>
<td>David M. Aronoff, MD</td>
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<tr>
<td>5:05 pm</td>
<td><strong>Kamran S. Moghissi, MD Lecture</strong></td>
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<tr>
<td></td>
<td>Syphilis in Pregnancy: New Concepts in Diagnosis and Treatment</td>
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<tr>
<td></td>
<td>Errol R. Norwitz, MD, PhD</td>
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<tr>
<td>5:45 pm–6:15 pm</td>
<td><strong>Closing Questions – Program Evaluation</strong></td>
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Lectures
THE STUDY AND MANAGEMENT OF THE HUMAN MICROBIOME

Thomas M. Schmidt, PhD

Tom Schmidt is a microbial physiologist and ecologist who has studied diverse microbes and microbial communities. Tom received a Ph.D. from The Ohio State University and conducted postdoctoral research at Scripps Institute of Oceanography and Indiana University. He spent much of his career studying the ecology of microbes in soil that are responsible for the exchange of greenhouse gases with the atmosphere. As director of the Microbial Diversity Course in Woods Hole, he introduced molecular approaches as a complement to traditional strategies to study the microbial world. He recently joined the University of Michigan where he has a joint appointment between the Departments of Internal Medicine and Ecology & Evolutionary Biology. That appointment reflects his expertise in applying ecological and evolutionary principles to understand the functioning of complex microbial communities, particularly those in the human microbiome. He is currently teaching a university course that merges his research and teaching goals by engaging students in a coordinated study of the effects of diet on the gut microbiome and directs a graduate program that combines laboratory sciences and modeling.
Michal A. Elovitz, MD

Michal A. Elovitz is a tenured Professor at the University of Pennsylvania, Perelman School of Medicine. She is Vice Chair of Translational Research. She serves as the inaugural and current Director of the Maternal and Child Health Research Center (MCHRC) at PENN. Dr. Elovitz has been funded by National Institute of Child Health and Development, National Institute of Nursing Research, National Institute for Mental Health, National Institute for Allergy and Infectious Disease, the National Heart, Lung and Blood Institute, Burroughs Wellcome Fund and the March of Dimes. For the last 18 years, Dr. Elovitz has been at the forefront of preterm birth research. Her development of mouse models to study the mechanisms involved in the pathogenesis of preterm birth and brain injury are used internationally to further the field. Her work on the role of the cervix, cervical remodeling and host immune-microbiome interactions in the cervicovaginal space as essential steps in the pathogenesis of preterm birth have provided new insight to the field. These findings provide novel opportunities for screening and therapeutic strategies to decrease the burden of preterm birth. Dr. Elovitz has made significant contributions to Maternal and Child Health through her individual research, the research supported by the Maternal and Child Health Research Center that she directs, and her active mentoring role to many faculty, fellows and students. She serves as a national member of the American Board of Obstetrics and Gynecology for the Maternal Fetal Medicine Division. She has served as a standing member on NIH study section and continues to serve frequently as an ad-hoc member to various study sections. She serves as special content advisor to the American Journal of OBGYN for translational research and as an Associated Editor for the Journal of Reproductive Sciences.
VAGINAL MICROBIOME IN PREGNANCY AND PRETERM BIRTH

Gregory A. Buck, PhD

Gregory A. Buck, Ph.D., is Professor of Microbiology and Immunology and Computer Science and Director of the Center for Microbiome Engineering and Data Analysis at Virginia Commonwealth University. He obtained a BS in Genetics from the University of Wisconsin-Madison, and his MS and Ph.D. in Microbiology and Immunology from the University of Washington-Seattle studying the toxinogenic bacteriophages of Corynebacterium diphtheriae. He did postdoctoral research at the Institute Pasteur in Paris studying the genetics of antigenic variation in African Trypanosomes, and subsequently joined the faculty in the department of Microbiology and Immunology at VCU. He founded VCU’s Nucleic Acids Research Facilities which maintains VCU’s Next Generation Sequencing infrastructure, and Center for High Performance Computing which provides research computing capacity to VCU’s investigators. He founded the Center for Microbiome Engineering and Data Analysis at VCU in 2018. Dr. Buck’s recent work has focused on high throughput microbial genomics and metagenomics, with a focus on evaluating the impact of the vaginal and related microbiomes on women’s health and pregnancy.
ASSESSMENT OF VAGINAL MICROBIOTA-HOST INTERACTIONS IN PRETERM BIRTH

David A. MacIntyre, PhD

Dr. David MacIntyre is a Senior Lecturer in Reproductive Systems Medicine in the Institute of Reproductive and Developmental Biology, Imperial College London. His research is focused on investigating the dynamic relationship between microbiota of the reproductive tract and the maternal host during pregnancy and understanding how this relationship impacts upon pregnancy outcomes and risk of preterm birth. This is achieved through the application of “systems” modelling approaches that involve integration and analysis of genomic, transcriptomic, microbiomic and metabolic profiling data. It is hoped that will lead to improved diagnostic and predictive tools that will assist in patient stratification and ultimately, improved pregnancy outcomes.
IS THERE A PLACENTAL MICROBIOTA?

Kevin R. Theis, PhD

Dr. Theis is an assistant professor in the Department of Biochemistry, Microbiology and Immunology in the Wayne State University School of Medicine. He is a broadly trained behavioral, evolutionary, and microbial ecologist who received his dual doctoral degree in Zoology and Ecology, Evolutionary Biology, and Behavior from Michigan State University in 2008, working in the laboratory of Dr. Kay Holekamp. He did his postdoctoral research in animal-microbial ecology in the laboratory of Dr. Thomas Schmidt, also at Michigan State University. Before joining the faculty at Wayne State University, Dr. Theis was a research assistant professor in the Department of Internal Medicine at the University of Michigan. His research focuses on host-microbe interactions. Specifically, his laboratory is determining whether paradigms of sterility in perinatal medicine need to be reconsidered, and whether we can effectively manage the human microbiome in the context of maternal-fetal health and disease.
RALSTONIA INSIDIOSA: A BLACK SWAN AT THE MATERNAL FETAL INTERFACE?

Indira U. Mysorekar, PhD

Indira Mysorekar, PhD is The James P Crane Professor of Obstetrics and Gynecology; as well as Pathology and Immunology. She is also the Director of the Center for Reproductive Health Sciences (CRepHS) at Washington University School of Medicine (WUSM), which she was instrumental in establishing in 2016 as a hub for outstanding translational research in women’s and reproductive health at WUSM. She has recruited fellows and medical students to foster their interest in OB/GYN and promote interest in women’s health and maternal-fetal health throughout their lifetime. She has helped to integrate basic and clinical research in the department by identifying and promoting the common space and bridging gaps. These efforts have been very fruitful as can be judged by the fact that the Department was ranked 2nd in NIH funding among all Obstetrics and Gynecology Departments at US medical schools in 2018. Dr. Mysorekar was awarded the Pathway to Independence Award and multiple R01s; and P20s; Burroughs-Wellcome Fund Investigator in Reproductive Sciences and March of Dimes Investigator in Prematurity Research. She has served in several leadership positions: as reviewer for large center review panels and study sections (MAPP Network, Developmental Centers for Benign Urology Research, KMBD, NIDDK); (Rapid Assessment of Zika Virus (ZIKV) Complications, NIAID) and is a Standing Member on the Pregnancy and Neonatology study Section, NICHD and a very active member in the Society of Reproductive Investigation as well as American Society for Reproductive Immunology. She has also been helping to facilitate the development of a women’s health center in Ethiopia, building on her own background as a young student in Tanzania, to serve as a role model for young African medical and graduate students. Dr. Mysorekar was awarded Outstanding Faculty Mentor Award at WUSM, as well as Mentor of the Year award in 2019 from WUSM Graduate Student Senate.
THE ENDOMETRIAL MICROBIOTA AND ITS IMPORTANCE IN REPRODUCTIVE SUCCESS

Carlos A. Simón, MD, PhD

Board Certified and Professor of Ob/Gyn at the University of Valencia, Spain; Adjunct Professor, Baylor College of Medicine, USA & Head of Scientific Advisory Board of Igenomix. His main interest is the understanding of the human embryonic implantation process, the maternal endometrium, and the cross-communication between them using different scientific perspectives. He is author of 453 publications in international peer-review journals, adding up to an accumulated impact factor of 2,163.73. His papers have received a total of 30,872. His H-Index is 99 (Google Scholar) and he is editor of 19 books (one best seller and one awarded as Highly Commended, BMA Book Awards 2018). He has been Director of 38 PhD Thesis. His work has been recognized by the ASRM, SRI, the Spanish Society of Obstetrics & Gynecology, and the Spanish Fertility Society. He received the Prize Jaime I and the ASRM Distinguished Research Award in 2016.

Google Scholar: https://scholar.google.es/citations?user=nA_MhRMAAAJ&hl=es
Website: www.carlos-simon.com
INTRA-AMNIOTIC INFLAMMATION AND INFECTION: CLINICAL DIAGNOSIS AND SIGNIFICANCE

Marian Kacerovsky, MD, PhD

Marian Kacerovsky, MD, PhD received his Medical Degree at Charles University, Faculty of Medicine in Pilsen, the Czech Republic in 1996. He got specialization in Obstetrics and Gynecology and in Maternal Fetal Medicine. He obtained his PhD at Charles University, Faculty of Medicine in Hradec Kralove, Czech Republic in 2012. Marian Kacerovsky worked for 8 years as a Head of the Perinatology Center in the Department of Obstetrics and Gynecology, University Hospital Hradec Kralove, the Czech Republic. His research group, studying host intraamniotic inflammatory response in pregnancies complicated by preterm prelabor rupture of membranes is located in Hradec Kralove, Czech Republic. Since May 2019, he has been working as a professor – research at the Perinatology Research Branch (NICHD/NIH), Wayne State University, Detroit. Marian Kacerovsky has published more than 150 original papers.
TREATMENT OF INTRA-AMNIOTIC INFECTION IN PRETERM LABOR, CERVICAL INSUFFICIENCY AND PRETERM PROM

Roberto Romero, MD, DMED, SCI

Roberto Romero, MD, D.Med.Sci., is Chief of the Perinatology Research Branch of the NICHD/NIH. He trained in Obstetrics and Gynecology and Maternal-Fetal Medicine at Yale University, where he was Director of Perinatal Research, before joining NIH. Dr. Romero’s team has made seminal contributions to the diagnosis and treatment of ectopic pregnancy, prenatal diagnosis of congenital anomalies, prediction and prevention of preterm labor/delivery, and the role of infection/inflammation in preterm and term parturition. In addition, Dr. Romero is an author of over 1000 peer-reviewed publications and several books, including the medical best seller, Prenatal Diagnosis of Congenital Anomalies. He is an elected member of the National Academy of Medicine and the recipient of 16 Doctorate Honoris Causa and Honorary Professorships from Universities worldwide. Dr. Romero has been honored by national and international professional societies for his medical and scientific contributions, including the Ian Donald Gold Medal (International Society of Ultrasound in Obstetrics and Gynecology), the Erich Saling Award from the World Association of Perinatal Medicine, the Maternité Prize in Obstetrics, awarded by the European Association of Perinatal Medicine, and also, is the first obstetrician to receive the prestigious Asan Award in Medicine from the Asan Foundation in South Korea. Dr. Romero is Editor-in-Chief for Obstetrics of one of the oldest journals in its discipline, the American Journal of Obstetrics & Gynecology. The journal has a circulation of 42,000 in the United States and has published seminal work that has changed the lives of mothers and children.
Jack D. Sobel, MD

Jack D. Sobel, MD is Dean of the School of Medicine at Wayne State University, previously Chair of Internal Medicine and served as Chief of Division of Infectious Diseases and Distinguished Professor of Medicine at Wayne State University School of Medicine. A graduate of the University of Witwatersrand, Johannesburg, South Africa. Dr. Sobel did his fellowship in Infectious Diseases at the National Institute of Health, Bethesda, Maryland and the Medical College of Pennsylvania. He is a board certified internal medicine specialist in the United States, the United Kingdom, Israel and South Africa and became a Master in the American College of Medicine in 2013. He has specialized as a “Candidologist”, specifically in Candida infection of the genitourinary tract. His research interests have encompassed microbiology, immunology and molecular biology of Candida infections including immunologic studies as well as tissue culture methods and development of animal models of experimental vaginal candidiasis. After more than a decade of studying systemic candidiasis and candidemia, he was the first to describe and report multi-drug resistant vaginitis due to a variety of Candida species as well as developing new treatment protocols. Over the last decade, his attention focused on other vaginal inflammatory conditions, notably recurrent and refractory bacterial vaginosis and immune mediated auto-inflammatory vaginitis focusing on the role of the vaginal microbiome in the pathogenesis of vaginal diseases. His ground-breaking treatments are the standard of care throughout the world and millions of women have benefitted from his innovative therapeutic regimens. He is the author of numerous peer-reviewed manuscripts, several books and book chapters. In viewing his career contributions while Chief of Infectious Diseases at Wayne, more than 70 ID fellows graduated as specialists. Serving as Dean of the largest medical school in North America for the last 5 years has not diminished his passion or commitment to infectious diseases involving the lower genital tract of women, and challenging the task of educating medical students in the modern era.
TRICHOMONIASIS

• >7 million cases annually in U.S
• Overall prevalence in U.S. is 3.2%
  • 1.3% N.H. White
  • 13.3% N.H Black
• Most prevalent in adolescent and young adults BUT.....
• Resistance fortunately rare (2.5% - 10%)

Patel et al Clin Infect. Dis. 2018

GLOBAL PREVALENCE OF TRICHOMONIASIS

• Prevalence varies geographically
  • 2016 review of 75 studies of STI’S
    Prevalence ranged from 3.9-24.6%
    Highest rates in low-middle income countries
• Prevalence of 20% among HIV-Infected women in South Africa and Zimbabwe

Price CM et al. S.T.D. 2018
Teasdale CA, PLOS ONE, 2018
DIAGNOSIS OF TRICHOMONIASIS
• Clinical
• Microscopy
• Culture
• DNA probe
• Molecular Testing

DIAGNOSIS OF TRICHOMONIASIS
3 FDA approved T. vaginalis NAATS
• Aptima (Hologic)
  Sensitivity 88-100%
  Specificity 98-100%
• BD Prob Tec (BD)
  Urine, endocervical swabs
• Xpeat TV assay (Cepheid)
  Potential for POC testing

COMPLICATIONS OF VAGINAL TRICHOMONIASIS
• Higher rates of Pelvic Inflammatory Disease ¹
• Poor birth outcomes ²

¹Moodly P. Clin. Inf. Dis. 2002
TRICHOMONAS AND PERINATAL MORBIDITY

• ↑ preterm birth (RR, 1.42)
• PPROM (RR 1.41)
• Small for gestational age (RR1.51)

Silver B.J. Sex. T. Dis. 2014

TREATMENT – CDC Guidelines 2015

• Metronidazole 2g orally S.D.
  or
• Tinidazole 2g S.D.

TREATMENT – 2020 CDC

• Metronidazole orally 500mg 7 days
• Similarly tinidazole!
  Why?  ↑ resistance – No
  ↑ recurrence / relapse
  ↑ persistence
**TREATMENT OF PREGNANT WOMEN WITH TRICHOMONIASIS**

- Symptomatic – Nitroimidazole 500 mg, bid x 7 days
- Asymptomatic – 2015 – Counsel regarding risks and benefits 2020 – Treat!

---

**TRICHOMONIASIS IN PREGNANCY**

- RCT of treatment of asymptomatic pregnant with trichomoniasis (Klebanoff MA.....NEJM 2001)
- Two 2 gm doses of MT248 hours apart between 16-23 and 24-29 weeks versus placebo.
- Higher risk of preterm labor

---

**TRICHOMONIASIS IN PREGNANCY**

Several limitations to study
- Atypical MTZ dosing
- 2nd round of MTZ given between 24-29 weeks – whereas greatest increase PTD was 35-36 weeks
- Causation?
TRICHOMONIASIS IN PREGNANCY
Lazenby: Unexpectedly high rates of PERSISTENT T. vaginalis (44% at >21 days) following treatment in pregnant women in Southern USA.

Lazenby G.B. et al. S.T.D. 2019

TREATMENT OF TRICHOMONIASIS
• HIV+ trich+ found 7 days MTZ more effective than SD at TOC.
• HIV-women similar results.

Kissinger P. et al. J. Acquired IDS 2010
Muzny CA et al. S.T.D. 2019

SHOULD PREGNANT WOMEN BE SCREENED FOR TRICHOMONIASIS?
• *Only population for routine screening in US is HIV infected women
• No recommendation for screening asymptomatic pregnant women. (Reserve for high risk)

Diagnostic testing for TV is recommended for pregnant women seeking for vaginal discharge, but should be considered in high prevalence settings. CDC

No ↑ risk of teratogenicity with use of MTZ (class B) during pregnancy.

*Sheehy O. 2015*

**NO AVOIDANCE OF ALCOHOL?** *(2020 Guidelines)*
MICROBIOME AND RISK OF TRICHOMONIASIS
Risk of acquiring trichomoniasis linked to specific vaginal bacteria

- BV
- Risk ↑ associated with
  - Prevotella amnii (RR 2.6)
  - Snethia Sanguinegens

Jarrett O.D. et al J.I.D. 2019

ASSOCIATION BETWEEN TRICHOMONIASIS AND BACTERIAL COMMUNITY
- T. vaginalis associated with CST IV, vaginal microbiota consisting of low proportions of lactobacilli and high proportion of Mycoplasma, Parvimonas, Snethia and other anaerobes
- Association? Causal


ASSOCIATION BETWEEN VAGINAL MICROBIOTA & MTZ TREATMENT OF TRICHOMONIASIS
High Nugent score predicted early failure of MTZ S.D treatment of trichomoniasis.

Gatski et al. Sex. Trans. Inf. 2011
VULVOVAGINAL CANDIDIASIS (VVC) IN PREGNANCY

EPIDEMIOLOGY

- Vaginal colonization rates ↑ in pregnancy 20 – 30%
- Vaginitis rates similarly ↑ particularly in 2nd and 3rd trimester.
- Rare intra-amniotic infection

Sobel JD. Lancet 2007

MICROBIOLOGY

- Poorly studied
- Little evidence to suggest change – or ↑ in Non-albicans Candida.
- Although ↑ in reported C.albicans fluconazole resistance such resistance rare in pregnancy (1/90) ......Why?
**DOES MODERATE TO HEAVY CANDIDA COLONIZATION INFLUENCE PREGNANCY?**

- Cotch study 1998 - multicenter cohort of 13,914 women
  - 83% C. albicans
  - Likely black or Hispanic
  - Prevalence midgestation 10%

No association with adverse pregnancy outcome

*Cotch MF et al. AM. J. Ob-GYN 1998*

---

**VVC AND PRETERM DELIVERY**

- Several studies demonstrate association between asymptomatic colonization and between VVC and PTD.
  - Kiss H (2004)
  - Roberts CL (2011)
- Unfortunately major methodologic flaws.

*Kiss H 2010, Roberts CL 2011, Czeizel AE 2004*

---

↓ in PTB when such colonization is treated with Clotrimazole
VVC AND PRETERM DELIVERY

• 2005–2014, N= 8447
• 1142 women asymptomatic *C.albicans* infection (13.5%)
• 185 women had recurrent (2.2%) positive smears.
• ↑ preterm delivery, ↑ LBW in RVV
• Routine screening and treatment recommended.

*Farr A et al. 2015*

At present screening for and treatment of VAGINAL ASYMPTOMATIC Candida colonization in pregnancy is NOT INDICATED

*Workowski K. CDC 2015*

TREATMENT OF VVC IN PREGNANCY

• No systemic / oral azoles
• Only topical azoles (clotrimazole, miconazole)
• Nystatin also Alternative

*Workowski 2015*
FLUCONAZOLE USE IN PREGNANCY

~4% of pregnant women in US use fluconazole.


Pregnancy and VVC - Fluconazole

• Early studies: No ↑ risk of longenital malformation (except in high doses)
  - Mastroiacova 1996
  - Wilton 1998
  - Jick 1998
  - Norgaard 2008

• Multiple studies evaluated antymycotic use in pregnancy
• Systematic review of fluconazole in first-trimester of pregnancy¹:
  - OR 1.10 (95% CI 0.98–1.25) for overall malformations
  - OR 1.29 (95% CI 1.05–1.58) for heart defects
  - OR 1.25 (95% CI 0.88–1.77) for craniofacial defects
  - OR 0.82 (95% CI 0.59–1.13) for limb/musculoskeletal defects
  - Craniofacial defects disappeared when 1 Danish study removed
• National Birth Defects Prevention Study² (subject to recall bias)
  - OR 5.53, 95% CI 1.68-18.24 for cleft lip/palate
  - OR 7.56, 95% CI 1.22-35.45 for transposition of the great arteries

¹ Alsaad Reprod Toxicol 2015
² Howley Am J Obstet Gynecol 2016
Pregnancy and VVC

- Danish nationwide registry\(^1\):
  - Increased risk of spontaneous abortion (HR 1.48, 95% CI 1.23-1.77) with fluconazole use
  - No increased risk with topical azole use or fluconazole use in the year prior to pregnancy

- Quebec Pregnancy cohort compared women exposed to fluconazole 150 mg (345 cases), fluconazole >150 mg (249 cases) and unexposed women\(^2\):
  - Fluconazole 150 mg associated with spontaneous abortion: OR 2.23, 95% CI 1.96-2.54
  - Fluconazole >150 mg associated with spontaneous abortion: OR 3.20, 95% CI 2.73-3.75
  - Fluconazole >150 mg associated with cardiac septal closure defects (OR 1.81, 95% CI 1.04-3.14)

\(^1\)Mølgaard-Nielsen JAMA 2016
\(^2\)Bérard CMAJ 2019

PREGNANCY AND VVC – FLUCONAZOLE
(Sweden, Norway)

No ↑ risk of STILL BIRTH or Neonatal Death

Pasternak B (2018) Jama

ASSOCIATION BETWEEN MATERNAL VAGINAL AND INFANT ORAL COLONIZATION

- Standard of care to screen and treat (Germany)
- Questionable association – non-maternal sources more likely.
Bacterial Vaginosis (BV)

- Most common vaginal cause of vaginal discharge
- U.S. prevalence 30% per NHANES data
- Associated with preterm birth, low birth weight, post-operative gyn infections, and increased risk for acquisition and transmission of HIV and STIs
- Characterized by depletion of lactic acid-producing lactobacilli and increases in BV-associated bacteria (BVAB) (Gardnerella vaginalis, Prevotella spp., Atopobium vaginae, BVAB1-3, Megasphaera spp., Sneathia spp., etc.)


Global Burden of BV

Annual global economic burden of treating symptomatic BV is US$4.8 (95% CI, US$3.7-6.1) billion

Sex Transm Dis 2019;46(5):304-311

Epidemiology of BV Strongly Supports Sexual Transmission of BV-Associated Bacteria (BVAB)

- BV associated with inconsistent condom use and increased numbers of recent and lifetime sexual partners
- Women with BV have an earlier median age of sexual debut than women without
- Most significant risk factor for incident BV is a new sexual partner while that for recurrent BV is a regular sexual partner
- High level of concordance of BV found in women and their female sexual partners

Epidemiology (2)

- Men with community state types (CSTs) 4-7 in their penile microbiota significantly more likely to have a female partner with a high Nugent score.\(^1\)
- Penile microbiota of male partners significantly more similar to the vaginal microbiota of their female partners, compared to other non-partner women, regardless of circumcision status.\(^2\)
- Detection of PSA among women positively associated with BV recurrence.\(^3\)

\(^1\)MBio 2015; 6(3):e00589; \(^2\)Microbiome 2016; 4:16; \(^3\)Sex Transm Dis 2016;43(3):172-6

Epidemiology (3)

- Partner concurrency significantly associated with prevalent BV.\(^1\)
- Among WSW with incident BV versus those without, the relative rate of any sexual activity prior to incident BV was 40% higher (p=0.010), digital-vaginal sex 57% higher (p=0.005), and digital-anal sex 5.6 times higher (p<0.001).\(^2\)
- In a systematic review of male circumcision and STIs & BV, male circumcision was found to result in lower BV prevalence in women.\(^3\)

\(^1\)Sex Transm Inf 2018; 94(1):75-77; \(^2\)Sex Transm Infect 2019, Mar 14 e-published online; \(^3\)Front Public Health 2019; 7:4

Traditional Diagnosis of BV

- Amsel criteria (clinical criteria)
  - Homogenous vaginal discharge, vaginal pH>4.5, positive whiff test, >20% clue cells/hpf
  - 3 out of 4 criteria needed for diagnosis
  - Sensitivity 37-70%, specificity 94-99% compared to Nugent

- Nugent score (vaginal Gram stain criteria)
  - 0-3: lactobacillus predominate vaginal microbiota
  - 4-6: intermediate microbiota with emergence of G. vaginalis
  - 7-10: disappearance of lactobacilli with numerous G. vaginalis and strict anaerobes
  - Mainly used in research settings

\(^1\)Am J Med 1983;74:14-22; \(^2\)Clin Microbiol 1991;29:297-301; Photos taken by Charles Rivers, PhD, MSPH
Direct Probe Assays

- **Affirm™ VPIII assay (BD)**
  - FDA approved test
  - Oligonucleotide probe test that detects high concentrations of *G. vaginalis* nucleic acids (>5 X 10^5 CFU of *G. vaginalis*/mL of vaginal fluid) to diagnose BV
  - Sensitivity 90%, specificity 97% compared with detection of clue cells on wet mount
  - Sensitivity 94%, specificity 81% compared with Nugent
  - Most useful in symptomatic patients in conjunction with vaginal pH and presence of amine odor (increases sensitivity to 97%)
  - Assay also has ability to diagnose *Candida* spp. and *T. vaginalis*
  - Results in ~30 minutes

*J Clin Microbiol 2018;56(9)*

Markers for Consideration in BV Nucleic Acid Amplification Tests

- Targeted PCR assays were developed for 17 vaginal bacterial species
  - Species selected based on their abundance in broad-range 16S rRNA gene clone libraries, their initial apparent specificity for BV, or their novelty
  - Applied to 264 vaginal fluid samples from 81 subjects with and 183 subjects without BV
  - Results compared to Amsel, Nugent

*J Clin Microbiol 2007; 45:3270-3276*

**Key Question:** Considerations of the currently recommended BV therapy in non-pregnant women?

- **Recommended**
  - Metronidazole 500 mg orally BID X 7 days
  - Metronidazole gel 0.75%, one applicator (5g) intravaginally, daily X 5 days
  - Clindamycin cream 2%, one applicator (5 g) intravaginally qhs X 7 days

- **Alternative**
  - Tinidazole 2 g orally once daily X 2 days
  - Tinidazole 1 g orally once daily X 5 days
  - Clindamycin 300 mg orally BD X 7 days
  - Clindamycin ovules 100 mg intravaginally qhs X 3 days

*2015 CDC STD Treatment Guidelines*
Updates to BV Treatment in Non-Pregnant Women

• There are no new data suggesting superior efficacy of new medications compared to currently recommended BV therapies.
• There are no new data demonstrating superiority of oral vs. topical treatment.
  • Topical medications will not impact the GI microbiota.
• 3 new BV medications are now FDA approved and available in the US
  • Clindesse 2% intra-vaginal cream X 1 dose (FDA-approved 2004 but not available in US until recently)
  • Metronidazole 1.3% vaginal gel X 1 dose (FDA-approved April 2014)
  • Secnidazole 2 g oral granules X 1 dose (FDA-approved September 2017)

Is there a role for vaginal probiotics in BV treatment?

• A previous Cochrane systematic review\(^1\) and Clin Microbiol Infect 2007;13(7):657 did not find sufficient evidence for or against probiotics for BV treatment
• There have been several small studies recently published regarding the use of vaginal probiotics (i.e. Elsharkawy et al. J Matern Fetal Neonatal Med 2019), many of which did not have a control group or were poorly powered.
• There is no recently published data on L. crispatus CTV-05 (LACTIN-V).
• The use of vaginal probiotics in the treatment of BV cannot be made at this time.

\(^1\)Cochrane Database Syst Rev 2009 Oct 7;(4):CD006289

Key Question: Do any changes need to be made to currently recommended BV therapy in pregnant women?

• There are no new data to suggest superior efficacy of new medications compared to currently recommended medications.
• There are no adequate and well-controlled studies of Clindesse in pregnant women. The FDA package insert for Clindesse states that it should only be used during pregnancy if clearly indicated.
• There are no adequate and well-controlled studies of 1.3% MTZ vaginal gel in pregnant women.
• There are no adequate and well-controlled studies of SEC in pregnant women.
Should pregnant women with asymptomatic BV who are at low risk for preterm delivery be treated?

- PREMEVA study: a large, multi-center RTC, concluded that low-risk asymptomatic pregnant women should not be screened or treated for BV.
- RCT of pregnant women with elevated vaginal pH ≥5.0 randomized to Clindamycin 300mg po BID for 5d vs. placebo.
  - Preterm birth (PTB) rates were similar in both arms: 13.9% Clindamycin vs. 13.1% placebo.
  - This study concluded that oral Clindamycin does not prevent PTB in women with elevated vaginal pH.
- No new data to suggest alteration of current guidance.

\[1\text{Lancet}\ 2018;\ 392(10160):2171-2179; \ 2\text{BJOG}\ 2018;\ 125(12):1601-1609\]

Should pregnant women with asymptomatic BV who are at high risk for preterm delivery be treated?

- No new data.
- 7 trials have previously evaluated treatment of pregnant women with asymptomatic BV at high risk for preterm delivery (mixed results) and are listed in the 2015 guidelines: one showed harm, two showed no benefit, and four demonstrated benefit.

Key Question: any new data on management of sexual partners of women with BV?

- One recent study assessed the acceptability and tolerability of topical and oral antimicrobial therapy in male partners of women with BV, including the impact of dual partner treatment on the vaginal and penile microbiota at baseline (day 0), day 8, and day 28.

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Location</th>
<th>Sample size</th>
<th>Treatment in females*</th>
<th>Treatment in male partners</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plummer et al. (2018)</td>
<td>Melbourne, Australia</td>
<td>16</td>
<td>Oral MTZ 400 mg twice daily for 7 days</td>
<td>Oral MTZ 400 mg twice daily for 7 days PLUS 2% clindamycin cream topically to the head of the penis and upper shaft (under the foreskin if uncircumcised) twice daily for 7 days</td>
<td>Acceptability and tolerability</td>
</tr>
</tbody>
</table>

*2% vaginal clindamycin cream as one applicator vaginally for 7 nights if MTZ was contraindicated

Impact on penile microbiota
- From day 0 to day 8, the most significant reductions were observed for Parvaglobus, Peptoniphilus, and Anaerococcus spp., resulting in decreases in prevalence between 68-75%.

Acceptability in male partners
- 14 (88%) took over 90% of tablets
- 11 (69%) applied over 90% of clindamycin doses
- Well-tolerated, few adverse events

Need larger studies with longer follow-up of men.

THE VAGINAL MICROBIOME AND GROUP B STREPTOCOCCAL PATHOGENESIS: INSIGHTS FROM A MOUSE MODEL

Amanda L. Lewis, PhD

Dr. Amanda Lewis is an Associate Professor of Molecular Microbiology and Obstetrics and Gynecology at Washington University School of Medicine. Her research program blends two research areas, glycobiology and women’s infectious disease, to explore concepts involving the relationships of microbes to each other and the varied niches of the female genitourinary system. She has held several NIH grants and has been recognized by investigator awards from the International Glycoconjugate Organization, March of Dimes, Burroughs Wellcome Foundation, and was named as a Distinguished Investigator by Washington University. This seminar will focus on the impact of a common member of the vaginal microbiome on the pathogenesis of group B Streptococcus using a mouse pregnancy model.
GROUP B STREPTOCOCCUS INFECTION IN PREGNANCY

David M. Aronoff, MD

David M. Aronoff, MD is the Director of the Division of Infectious Diseases at the Vanderbilt University School of Medicine and the founding Director of the Vanderbilt Pre³ Initiative (Preventing adverse Pregnancy outcomes and Prematurity). He received his Bachelor of Science degree in Microbiology from Indiana University and his Medical Degree at Tufts University in Boston. He completed internship and residency training, as well as clinical fellowship in Infectious Diseases in Internal Medicine and research fellowship in Clinical Pharmacology at Vanderbilt University. He then joined the faculty in Infectious Diseases at the University of Michigan where he also completed a research postdoctoral fellowship in Immunology. He returned to Vanderbilt in 2013 as Director of the Division of Infectious Diseases in the Department of Medicine with secondary faculty appointments in the Department of Pathology, Microbiology, & Immunology and the Department of Obstetrics & Gynecology. He is also a faculty member in the Vanderbilt Center for Medicine, Health and Society and an Adjunct faculty member in the Department of Microbiology and Immunology at Meharry Medical College. Primary areas of focus include mechanisms of disease pathogenesis involved in GBS infections causing chorioamnionitis, preterm birth, stillbirth and neonatal sepsis.
Research support from Pfizer, NIH, March of Dimes

Advisory Board/Consultant:
- ABEL Therapeutics
- Bioceutics, LLC
- BIC USA
- NAEJA - RGM
- Cepheid
- Synthetic Biologics

I will be discussing research funded by NIH & March of Dimes

Disclosures

Outline

• Group B Streptococcus (GBS)
• Chorioamnionitis
• Our studies of bacterial infection in fetal membranes
• Future directions
Group B Streptococcus

- Nonmotile, Gram positive coccus
- Encapsulated
- 10 serotypes (6 cause most perinatal disease)
- Usually beta hemolytic
  - Hemolysis caused by a pigment important for virulence
- Colonize mucosal surfaces (GI, GU) tract
- Causes skin infections & infections during pregnancy

CDC's 2019 Antibiotic Resistance Threats Report. Strains resistant to vancomycin have been reported.
GBS Colonization

- Rectal/vaginal colonization the strongest risk factor for invasive infection
- On cross-section, 20-30% of pregnant women are colonized with GBS in the vagina &/or rectum
- A longitudinal study of South African women found that 50% of women are colonized at some point during pregnancy
- Colonization increases the risk for PPROM & preterm birth


Leading cause of neonatal sepsis in the Americas, Europe, Australia, & sub-Saharan Africa
- EOS: Early-onset neonatal sepsis (days 0-7)
- LOS: Late-onset neonatal sepsis (days 7-89)


GBS Neonatal Sepsis in the US
- 0.23 cases EOS per 1000 births
- 0.31 cases LOS per 1000 births
- EOS ~3x more common in babies born preterm
Most EOS Results from Intrauterine Inoculation

- 75.02% 0-24 hr
- 19.66% 24-48 hr
- 5.32% >48 hr

Time from birth to identification of sepsis
Total = 1277 EOS cases

Figure from Porta K, Rizzolo D. JAAPA. 2015 Mar;28(3):24-9.


• ~ 1 in 8 stillbirths associated with infection in the US
  - E. coli > GBS, Enterococcus leading pathogens
  - Most infections associated with chorioamnionitis
  - Similar to recent South African data
  - ~ 1 in 5 stillbirths associated with infection
  - GBS > E. coli > Enterococcus & S. aureus

GBS as a Cause of Stillbirth

Global Data

- 21.7 million pregnant women with live births colonized with GBS
- 320,000 infants with invasive GBS sepsis & meningitis
- 57,000 maternal invasive GBS infections (stillbirth)
- 33,000 maternal invasive GBS infections
- 35 million preterm births attributable to GBS

Data from Seale AC, et al. CID 2017:65 (Suppl 2)
Prevention

New Guidelines for Screening & Treating GBS

ACOG COMMITTEE OPINION
Number 782
(July 2019)
Committee on Obstetric Practice
Prevention of Group B Streptococcal Early-Onset Disease in Newborns

- Rectovaginal screening 36 through 37 weeks
- Effective at preventing early-onset neonatal sepsis (EOS)
- But exposes many women to antibiotics (NNT 400–1,800)
- Not perfect:
  - ~40% cases of GBS EOS born to women who screened negative
- Does not prevent LOS, preterm birth or stillbirth
- Vaccine is hopefully on the way

1. ACOG Committee Report, Obstet Gynecol (2017)
Pathogenesis

GBS is adept at causing intrauterine infection during pregnancy without causing symptoms until a bad outcome occurs.

A stealth bomber

Summary

The cellular & molecular mechanisms underpinning these processes are not clearly defined.
**Bacterial Causes of Chorioamnionitis**

<table>
<thead>
<tr>
<th>Organism Commonly Identified in Chorioamnionitis</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listeria monocytogenes</td>
<td>15-62</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>7-15</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>6-11</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2-12</td>
</tr>
<tr>
<td>Gardnerella vaginii</td>
<td>6-25</td>
</tr>
<tr>
<td>Eubacterium sp</td>
<td>6-10</td>
</tr>
<tr>
<td>Fusobacterium sp</td>
<td>10-67</td>
</tr>
<tr>
<td>Proteus sp</td>
<td>17</td>
</tr>
<tr>
<td>Peptostreptococcus sp</td>
<td>16</td>
</tr>
</tbody>
</table>


**Human Fetal Membranes**

What are the cellular & molecular events that lead to these complications?

3 Major Complications
1. Preterm labor
2. Membrane rupture
3. Stillbirth/neonatal sepsis

**Our Research**
Future Directions

- Identifying mechanisms of trophoblast-macrophage immunoregulation
- Defining the paracrine signaling cascades that lead to PPROM
- Identifying potential targets for prevention such as new vaccine targets or early diagnostic / prognostic biomarkers

Conclusions

- Despite preventive strategies, GBS remains an important cause of maternal-child morbidity & mortality
- Fetal membrane immunobiology & mechanisms of chorioamnionitis remain ill-defined
- We hope to identify new pathways to disease prevention & management that improve maternal-child health
- I will gladly email you my slides (daronoff@vumc.org)

Acknowledgments
Retrospective cohort study of all neonates diagnosed with GBS sepsis by culture & clinical findings within the first 72 hr of life

94 babies with GBS EOS: 93 diagnosed within 1 hr of delivery

EOS babies more likely preterm & born by cesarean

Chorioamnionitis rates higher in cases (42%) vs controls (8%)
KAMRAN S. MOGHISSI, MD LECTURE

SYPHILIS IN PREGNANCY:
NEW CONCEPTS IN DIAGNOSIS AND TREATMENT

Errol R. Norwitz, MD, PhD, MBA

Errol R. Norwitz, MD, PhD, MBA is the Louis E. Phaneuf Professor and Chair of Obstetrics & Gynecology at Tufts Medical Center and Tufts University School of Medicine in Boston. He completed his medical training at the University of Cape Town (South Africa), his PhD at Oxford University (England) on a Rhodes Scholarship, and his Ob/Gyn Residency and Maternal-Fetal Medicine Fellowship at Harvard University. He is a Founding Investigator of the Mother Infant Research Institute at Tufts Medical Center. He received his MBA from the Questrom School of Business at Boston University, and was appointed Chief Scientific Officer at Tufts Medical Center in 2016. Most recently, he was elected to the Board of Scientific Counselors of NICHD. He is the author of 14 textbooks, 90 book chapters, and more than 250 original research articles and reviews. His research has been supported by NIH/NICHD and March of Dimes as well as institutional and industry sponsors. His areas of research interest include the genetics of adverse pregnancy outcome and the molecular regulation of parturition, both at term and preterm.
SYPHILIS IN PREGNANCY

Disclosure

Errol R. Norwitz, MD, PhD, MBA

I have no financial relationships with a commercial entity producing healthcare-related products and/or services related to this presentation.

Objectives

- Recognize the risks of syphilis during pregnancy to both mother and fetus
- Understand the importance of screening for syphilis in pregnancy
- Discuss the antepartum, intrapartum, and postpartum management of patients with syphilis in pregnancy
**Pathogenesis**

- A systemic infection caused by a bacterium of spirochete family, *Treponema pallidum*
- Major concern in pregnancy because of the risk of transplacental infection and the serious sequelae of congenital syphilis
- Four stages of the adult form of the disease
  - Clinical features and disease progression are not altered by pregnancy

**Primary syphilis**

- Characterized by a single 1-2 cm painless ulcer (chancre) at the site of inoculation
  - Presents 2-3 weeks after initial contact
  - Typically on the penis or vulva (may be unnoticed if in vagina or on cervix)
  - HIV-positive patients may have multiple lesions
  - Resolves spontaneously in 3-6 weeks even in the absence of treatment
- May also have regional lymphadenopathy
  - Unilateral or bilateral
  - Typically mild

**Secondary syphilis**

- Disseminated systemic process
  - Occurs in 25% of untreated patients
  - Starts 6 weeks to 6 months after chancre
  - Resolves spontaneously in 2-6 weeks
- Clinical manifestations include:
  - Diffuse symmetric maculopapular rash on trunk, extremities, palms and soles
  - “Moth eaten” hair loss
  - Generalized lymphadenopathy
  - Condyloma lata on mucus membranes
  - Fever, weight loss, malaise
  - (Hepatitis, uveitis, synovitis, nephritis)
- Lesions are highly infectious
Latent syphilis

- Characterized by positive serology without symptoms
- Classified into:
  - Early latent (if there is a documented non-reactive syphilis test or history of early syphilis in the last year)
  - Otherwise, late latent (assume that more than 1 year has passed since initial infection)
- By definition, there are no clinical features
- The infection can be transmitted to a sexual partner or fetus, but less commonly

Tertiary (late) syphilis

- Only 35% of cases progress on to tertiary
- Typically 5-20 years after primary infection
- Characterized by slowly progressive signs and symptoms. Clinical features include:
  - Neurosyphilis (meningitis, dementia, ataxia, tabes dorsalis)
    -- If suspected, perform LP to exclude diagnosis
  - Cardiovascular syphilis (aortitis, saccular aneurysms)
  - Gumma (non-malignant granulomatous destructive lesions of skin, bone, mucus membranes, and liver)

How is syphilis acquired?

- Most adult cases are sexually transmitted
  - Spirochetes pass from active lesions across intact mucus membranes or abraded skin
  - Risk factors: race (AA), poor, young (<29 years), low SES, lack of prenatal care, illicit drug use, other STIs, sex worker, multiple sexual partners, live in area of high prevalence, male predominance in US (but male = female worldwide)
  - In US, 50% of women with syphilis have no identifiable risk factors*
- Efficiency of sexual (horizontal) transmission is approximately 30%**

Norwitz ER, Hicks CB. UpToDate (accessed Sept 3, 2019)
Epidemiology of adult disease

- **Syphilis occurs worldwide, but mostly in developing countries**
- **Rate decreased after introduction of penicillin**
  - Increased in 1980-90s with HIV epidemic
  - Recent resurgence in US with doubling from 2013 to 2017; 143% increase in rate in reproductive-aged women; highest in age 20-24 years (7.8 cases per 100,000 women)*


Epidemiology of congenital disease

- **Affects 1 million pregnancies/year worldwide**
  - Mostly in countries where mothers receive no prenatal care or insufficient treatment for syphilis
- **In US, prevalence peaked at 100 per 100,000 live births in 1991, declined, but has resurged in recent years**
  - In 2017, 914 cases in US (153% increase since 2013)
  - US rate of 23.3 per 100,000 live births in 2017 c/w global rate of 473 per 100,000 live births*


Vertical transmission

- **Modes of transmission**
  - Transplacental
  - Direct contact with infectious lesion at birth
  - **Not transmitted through breast milk (can be transmitted through bloody discharge/cracked nipples)**
- **Timing of transplacental transmission**
  - Can occur at any stage of pregnancy (after 9-10 weeks) and at any stage of the maternal disease
  - Higher rates of transmission occur with:
    - Early stage disease (50% for primary/secondary, 40% with latent, 10% with tertiary)*
    - Later gestational age
    - Failure to diagnose and treat disease

* Fiumara NJ. Clin Obstet Gynecol 1975; 18:183
Congenital syphilis

- Congenital syphilis is a devastating disease

- Clinical manifestations include:
  - Miscarriage
  - Perinatal death
  - Preterm birth
  - Fetal growth restriction
  - Congenital anomalies
  - Low birth weight
  - Active neonatal syphilis
  - Long-term sequelae, such as deafness and neurologic impairment

- Congenital syphilis is preventable

  - Low birth weight
  - Active neonatal syphilis
  - Long-term sequelae, such as deafness and neurologic impairment

Early congenital syphilis

- Defined as clinical manifestations <2 years

- Clinical features include:
  - Systemic features (fever, lethargy, hepatosplenomegaly, failure to thrive, edema)
  - Hematologic (hemolytic anemia, thrombocytopenia, leukopenia/leukocytosis)
  - Mucocutaneous (syphilitic rhinitis, maculopapular rash/desquamation, condyloma lata on mucosal surfaces)
  - Neurologic (acute leptomenigitis, chronic meningovascular syphilis with hydrocephalus, cranial nerve palsy, neurodevelopmental/intellectual deterioration)
  - Musculoskeletal (periostitis, “sawtooth metaphysis”, bone pain in legs with pseudoparalysis, demineralization of tibia)
  - Nephritis, jaundice, arthritis

Early congenital syphilis

- Syphilitic rhinitis (“snuffles”)
- Desquamation
- Rash
### Late congenital syphilis

**Defined as clinical manifestations >2 years**

**Clinical features include:**
- Facial features (frontal bossing, saddle nose, short maxilla, protuberant mandible, fissures in skin/rhagades)
- Eye (interstitial keratitis, chorioretinitis, glaucoma, corneal scarring, optic atrophy)
- Ears (sensorineural hearing loss)
- Mouth (Hutchinson teeth, mulberry molars, perforation of hard palate)
- Skin (gummas)
- Musculoskeletal (bowing/saber shins, painless arthritis, scaphoid scapula, enlargement of clavicular joints)
- Neurologic (seizures, hydrocephalus, intellectual disability, juvenile general paresis)

### Late congenital syphilis

- **Hutchinson teeth**
- **Mulberry molars**
- **Saber shins**
- **Rhadage** (angular cheilitis, skin fissures)

### Prenatal diagnosis

- **Prior to 20 weeks**
  - 40% of early infections will end in abortion if untreated
  - Fetal abnormalities rarely seen on ultrasound at this time because of fetal immunologic immaturity

- **After 20 weeks, ultrasound is non-specific**
  - Hepatosplenomegaly (70-80%)
  - Polyhydramnios (10%)
  - Placental maldigestion (30%)
  - Ascites or hydrops (10%)
  - Anemia / elevated MCA Doppler PSV (30%)

- **An abnormal ultrasound is not diagnostic**
  - Sensitivity ~40%

- **Darkfield microscopy of AF is rarely done**

Maternal screening

- Universal serologic screening is recommended for all pregnant women
  - At the first prenatal encounter
  - In high-risk patients, repeat at 28-32 weeks and at delivery
- Recent shift from ‘traditional’ syphilis testing algorithm to ‘reverse’ sequence syphilis screening (RSSS) algorithm
  - RSSS now recommended by CDC
  - Faster workflow, cheaper, fewer false-negatives
  - Both rely on a combination of non-treponemal (non-specific) and treponemal (specific, but not necessarily T. pallidum) tests

WHO. Sex Transm Dis 2007; 34:S22
CDC. MMWR Recomm Rep 2015; 64:1

Treponemal vs non-treponemal tests

- Treponemal tests
  - TPPA (Treponema pallidum particle agglutination assay)
  - TP-PA (Treponema pallidum particle agglutination assay)
  - TP-EIA (Treponema pallidum enzyme immunoassay)
  - TP-CIA (Chemiluminescence immunoassay)
- Non-treponemal tests
  - RPR (Rapid Plasma Reagin)
  - VDRL (Venereal Disease Research Laboratory)

CDC. MMWR Recomm Rep 2015; 64:1

‘Traditional’ syphilis testing algorithm

- Syphilis unlikely, or too early to detect
  - If clinical diagnosis points to treatment
  - If non-treponemal test is positive
- Syphilis unlikely if at risk, repeat RPR in several weeks
- Syphilis likely if present
  - Evaluate similarly
  - Past infection and treatment
  - Current infection risk
  - Administer therapy according to CDC’s Sexually Transmitted Disease Treatment Guidelines, 2016 if not previously treated

CDC. MMWR Recomm Rep 2015; 64:1
False-positive tests

- Biological false-positives—especially non-treponemal tests—are common in pregnancy (30-50%)
  - Typically lasts for 6 months
  - No further evaluation is needed (consider repeating postpartum)

- Common causes
  - Recent febrile illness
  - Recent immunization

- Other causes
  - SLE
  - Infections (Lyme, TB)
  - Transfusions
  - IVDA

Test comparison

<table>
<thead>
<tr>
<th>RPR</th>
<th>Treponemal Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inexpensive reagents</td>
<td>• ‘Expensive’ reagents</td>
</tr>
<tr>
<td>• Manual test</td>
<td>• Can be automated</td>
</tr>
<tr>
<td>• Subjective</td>
<td>• Objective (signal/cutoff ratio)</td>
</tr>
<tr>
<td>• Not scalable</td>
<td>• Easily scalable</td>
</tr>
<tr>
<td>• Hook effect ➞ false negative</td>
<td>• May not have hook effect</td>
</tr>
<tr>
<td>• Will miss latent syphilis</td>
<td>• Detects latent syphilis</td>
</tr>
<tr>
<td>• Absolutely required to monitor active infection</td>
<td>• Cannot be used to monitor active infection</td>
</tr>
</tbody>
</table>
Maternal treatment

- **Penicillin is standard of care for treatment in both pregnant and nonpregnant patients**
  - No penicillin-resistant strain of *T. Pallidum* has been identified
- **Penicillin is the only treatment recommended in pregnancy**
  - Other agents are either teratogenic (tetracyclines), do not cross the placenta and/or are ineffective in treating fetus (erythromycin, azithromycin), or lack efficacy data in pregnancy (ceftriaxone)
- In pregnancy, patients with penicillin allergy → skin testing, desensitization (oral or IV, usually inpatient), and penicillin treatment

Maternal treatment (cont.)

- **Treatment depends on stage of the disease**
  - Pregnancy does not affect maternal response to treatment
  - **Primary / secondary / early latent**
    - Single-dose Benzathine Penicillin G (2.4M units IM)
  - **Late latent / tertiary / unknown duration**
    - Multi-dose Benzathine Penicillin G (2.4M units IM weekly x 3)
    - Neurosyphilis typically requires inpatient IV therapy
- **Beware Jarish-Herxheimer Reaction**
  - Acute febrile reaction: headache, myalgia, rash, hypotension
  - Starts 1-2h after treatment, peaks at 8h, resolved 24-48h
  - Due to release of treponemal LPS and cytokine release
  - Can lead to preterm labor, nonreassuring fetal testing
  - Management is supportive care (antipyretics, IV fluids)

Post-treatment follow-up

- **Treat sexual contacts (single dose Pen G)**
- **Follow serial RPR/VDRL titers q 3 months**
  - A fourfold decline by 6 months (i.e., change in 2 dilutions say from 1:16 to 1:4) is an acceptable response in pregnancy
  - In nonpregnant patients, can wait 12 months for early disease or 24 months for late disease before retreatment
  - Same lab, same test (treponemal tests do not predict response)
  - If inadequate decline or a rise in titer → retreat
- **Curative for fetal infection in most cases**
  - Decreases congenital syphilis rates from 70-100% if untreated to 1-2% if adequately treated in pregnancy *
  - Decreases SB 82%, PTB/LBW 65%, NND 80%, infection 97%*

* Blencowe H, et al. BMC Public Health 2011; 11:S9
Norwitz ER, Hicks CB. UpToDate (accessed Sept 3, 2019)
Obstetric management

- **Fetal anatomy scan after 20 weeks looking for signs of congenital infection**
- **In fetuses with signs of congenital infection, consider weekly scans looking for resolution**
  - MCA Dopplers, ascites, polyhydramnios resolve in 1 month, then placentomegaly, lastly hepatosplenomegaly
  - IUT rarely needed
- **No change in intrapartum care**
  - Consider late preterm delivery if signs worsen or if hydrops
- **Notify pediatrics; send placenta to pathology**
  - Silver staining may reveal spirochetes, but may be difficult

Neonatal follow-up

- **Treat newborn**
  - Single-dose Benzathine Penicillin G (50,000 u/kg IM)
  - only if asymptomatic and no CNS involvement
  - Aqueous Penicillin G (50,000 u/kg IV q8-12h x 10 days)
  - Procaine Penicillin G (50,000 u/kg IM daily x 10 days)
- **Follow RPR / VDRL titers every 3 months**
  - Continue until titers decrease fourfold or test is non-reactive
  - Tiers should decline by 3 months, non-reactive by 6 months
  - A small number of patients will remain low-tier reactive for many years (know as a "serofast reaction")
- **Perform clinical exam at each visit for signs/symptoms of late stage syphilis**

Take home messages

- **Stages/diagnosis not altered by pregnancy**
- **All pregnant women should have serologic screening for syphilis at first prenatal visit**
  - Repeal screening at 26-32 weeks in women at high risk
- **Vertical transmission is highest in early stage disease and at later gestational age**
- **Penicillin is the only treatment recommended in pregnancy**
  - Highly effective: will treat maternal disease, prevent vertical transmission, and treat established fetal disease
  - A fourfold decline in RPR/VDRL titers by 6 months represents an adequate response in pregnancy
CONGENITAL SYPHILIS IS PREVENTABLE

IF SYPHILITIC MOTHERS WILL TAKE
Adequate Treatment During the
Last Few Months of Pregnancy

NEW YORK STATE DEPARTMENT OF HEALTH

NY State Department of Health, 1936
## SUNDAY, DECEMBER 8, 2019
### PROGRAM AGENDA

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30 am</td>
<td>Registration &amp; Continental Breakfast</td>
</tr>
<tr>
<td>7:50 am</td>
<td>Welcome / Opening Remarks</td>
</tr>
<tr>
<td></td>
<td><strong>MODERATOR: Kevin R. Thels, PhD</strong></td>
</tr>
</tbody>
</table>

### VIRAL INFECTIONS IN PREGNANCY

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 am</td>
<td>The Immune Response to Viruses and Its Importance in Pregnancy Complications&lt;br&gt;Gil G. Mor, MD, PhD</td>
</tr>
<tr>
<td>8:40 am</td>
<td>Preventing Perinatal HIV Infection: Getting From Good to Great&lt;br&gt;Theodore B. Jones, MD</td>
</tr>
<tr>
<td>9:20 am</td>
<td>Hepatitis B &amp; C in Pregnancy&lt;br&gt;Elizabeth J. May, MD, PhD</td>
</tr>
<tr>
<td>10:00 am</td>
<td>Cytomegalovirus Infection in Pregnancy&lt;br&gt;Suresh B. Boppana, MD</td>
</tr>
<tr>
<td>10:40 am</td>
<td>Overview of TORCH Infections&lt;br&gt;Karen E. Johnson, MD</td>
</tr>
<tr>
<td>11:20 am – 11:40 am</td>
<td>BREAK WITH EXHIBITORS</td>
</tr>
<tr>
<td></td>
<td><strong>CLINICAL ASPECTS OF INFECTION IN PREGNANCY</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>11:40 am</td>
<td><strong>KEYNOTE ADDRESS</strong>&lt;br&gt;Lethal Maternal Infections: Group A Streptococcus with Necrosis, Necrotizing Fasciitis&lt;br&gt;David A. Eschenbach, MD</td>
</tr>
<tr>
<td>12:20 pm</td>
<td>Maternal Sepsis: Diagnosis and Management&lt;br&gt;Muhammad Jaffar, MD</td>
</tr>
<tr>
<td>1:00 pm</td>
<td>Vaccination during Pregnancy: A Powerful Method to Prevent Infection&lt;br&gt;Bernard Gonik, MD</td>
</tr>
<tr>
<td>1:40 pm – 2:00 pm</td>
<td>CLOSING QUESTIONS – PROGRAM EVALUATION</td>
</tr>
</tbody>
</table>
Lectures
THE IMMUNE RESPONSE TO VIRUSES AND ITS IMPORTANCE IN PREGNANCY COMPLICATIONS

Gil G. Mor, MD, PhD

Gil G. Mor, MD, PhD is the John M. Malone Jr. MD, Endowed Chair Professor and Scientific Director of The C.S. Mott Center for Human Growth and Development at Wayne State University. His research interests focus on the immunology of pregnancy and the role of inflammation in cancer formation and progression. Dr. Mor was the Editor in Chief of the American Journal of Reproductive Immunology (2009-2019). He is the Senior Editor of a book series on Reproductive Immunology with Elsevier. He is the President of the American Society for Reproductive Immunology. Dr. Mor is the recipient of grant funding from the National Institute of Child Health Development (NICHD), National Cancer Institute (NCI) and National Institute of Allergies and Infectious Diseases (NIAID). He is widely published in the area of immunology and reproduction and is the editor of a three books on “Immunology of pregnancy” and “Apoptosis and Cancer”. Dr. Mor is member of the American Association for Cancer Research, the Society for Gynecologic Investigation, American Association of Immunologist and the American Society of Reproductive Immunology. He is also a member of the International Advisory Committee for the Sino-American Center of Translational Medicine and Honorary member and Professor of several scientific societies in Asia, South America and Europe.
PREVENTING PERINATAL HIV INFECTION: GETTING FROM GOOD TO GREAT

Theodore B. Jones, MD

Theodore B. Jones, MD, is a graduate of Morehouse College in Atlanta, GA. He received his medical degree from Temple University School of Medicine in Philadelphia and completed a residency in obstetrics and gynecology at Baylor University Medical Center in Dallas, TX. After serving for three years in the National Health Service Corps in rural southeast Arkansas, he completed a fellowship in Maternal Fetal Medicine at Wayne State University/Hutzel Hospital in Detroit MI. He has been a faculty member at Wayne State University School of Medicine (WSUSOM) since fellowship completion and is currently an Associate Professor. Department administrative posts have included Residency Program Director, Associate Chair for Education, interim Chair, Division Director for Maternal Fetal Medicine, and Chief of Obstetrics for Hutzel Women’s Hospital. Currently, he is Vice Chairman for WSU/Oakwood Programs in the Department of Obstetrics and Gynecology and Academic Chair and Residency Program Director at Oakwood Hospital and Medical Center in Dearborn MI. He is Medical Director and founder of the Perinatal Infectious Disease Clinic at the Detroit Medical Center University Health Center, the only obstetrical clinic for pregnant women with HIV infection in the state. Since 1999, there have been no infected babies born to mothers compliant with the clinic program. In addition, he is the obstetric principal investigator for perinatal HIV infection prevention studies sponsored by the International Maternal Pediatric and Adolescent AIDS Clinical Trial Network (IMPAACT), a NIH-funded network.
Preventing Perinatal HIV Infection: Getting from Good to Great

Theodore B. Jones, MD
Maternal Fetal Medicine and Fetal Imaging
William Beaumont Royal Oak MI
Director, Maternal Fetal Medicine
Beaumont Dearborn Hospital

No conflicts

Special thanks to Jonathan Cohn, MD
Infectious Disease
WSUSOM

Talk Objectives

• Review the demographics of the disease in the US.
• Update available testing strategies and the importance of universal screening.
• Discuss clinical considerations for achieving viral suppression and combination antiretroviral therapy (cART).
• Review evidence for optimal care in labor and delivery.
• Discuss management of HIV positive mothers and breastfeeding.
Women and HIV: Snapshot

- 20% (9500) of new HIV infections in 2010:
  - 21% decrease since 2008
- 8102 new AIDS diagnoses among women: 25% of diagnoses that year
  - a decline
- One quarter of deaths in 2010
- Heterosexual sex most common risk factor
  - 84% of new infections in 2010
- 6,000 to 7,000 HIV-positive women deliver annually
- Fewer than 200 HIV infected infants are now born in the US each year
  - 40% of HIV-infected infants born to mothers with unknown status

KFF: HIV and women fact sheet March 2014

Women and HIV: Snapshot (2)

- Women of color highly affected: new infections, living with HIV, and HIV-related deaths in US
- In 2010: 64% of new HIV infections in women occurred in Black women (only 13% of female pop.)
- HIV incidence higher in Blacks and Latinas than for white women (20x, 4x, respectively)
- HIV is 7th leading cause of death in black women

Pregnancy & HIV Testing in Michigan

- Two Tests, Two Lives
  - Test all women at in first trimester at diagnosis of pregnancy
  - Test all women at 3rd trimester starting at 28 weeks
  - Third test for high risk women at 36 weeks or onset of labor
- Confidentiality
  - Separate consent required in Michigan for release of HIV, mental health or substance use information
- Duty to Warn
  - Physicians must warn a known individual at risk from true exposures to an HIV infected patient
    - This responsibility can be transferred to the local health department
- Partner Services
  - Local health department will attempt to contact and inform all partners potentially exposed within the past year, without using the index client’s name, to offer HIV testing and referral
HIV Testing in Michigan

- In health care settings, written or verbal consent for HIV testing must be documented in the medical record
  - Written consent as part of the general consent to treatment is acceptable as long as the patient can consent to other treatment, but refuse HIV testing
- State funded test sites use written informed consent

[Link to Michigan FAQ on HIV Testing Consent]

HIV Diagnostic Testing

- Step 1: 4th generation HIV-1/2 Ag/Ab combo immunoassay (preferred but 3rd gen. acceptable)
- Step 2: HIV-1/HIV-2 antibody differentiation immunoassay
- Step 3: HIV-1 RNA assay

[Link to New York State guidelines for diagnostic testing]
Rapid testing at delivery for women with no PNC or HIV test

- High risk of perinatal transmission in women without prenatal care or prior HIV test
- **Rapid testing** in labor makes it possible to begin ART prophylaxis and refer mother for care
- Begin **ART prophylaxis asap after a positive rapid test** (before confirmatory test results are available)

Conception Planning for HIV-infected Women and Men

- Applies to men and women regardless of partner preferences
- Some newly diagnosed persons assume they can never have children, and this contributes to the challenge of adjusting to the new diagnosis.
- At the same time, about 50% of US pregnancies are unplanned
  - Contraception and pre-conception planning are not our society’s strong points

Getting Pregnant: HIV-infected couple

- Expert consultation! (AIII)
- Screen and treat any genital tract infections (AII)
  - HBV testing and vaccination (JC)
- Both partners should be on fully suppressive antiretroviral regimens before attempting to conceive (AII)
- Since TasP is not perfect, condom-less intercourse is only recommended during times of peak fertility, with use of condoms for other acts of intercourse
  - 2 days before and day of ovulation
  - (What about U=U?)
Getting pregnant: HIV serodifferent couple

HIV-infected male
- Assisted insemination with HIV negative donor sperm is safest (AIII)
- Sperm analysis of male prior to attempts to assure male fertility (AIII)
- Sperm preparation technique (BII)
  - Intrauterine fertilization
  - In vitro fertilization

HIV-infected female
- Condoms for intercourse
- Assisted insemination during peri-ovulatory time (AIII)
  - Medical intrauterine insemination
  - In your office
  - Home intravaginal insemination
  - “Turkey baster”

Getting Pregnant: HIV serodifferent couple, infected male partner

- Sperm analysis of male prior to attempts to assure male fertility (AIII)
- Antiretroviral therapy:
  - Undetectable HIV RNA in male on treatment (AI)
  - PrEPception by female starting 30 days prior to conception and continuing at least 30 days after.
    - Indicated if the male partner’s HIV RNA is unknown or not fully suppressed
    - Unclear how much benefit this adds if male has undetectable HIV RNA (BII)(See Hoffman et al model 2015)
  - Condomless intercourse only during peak fertility till conception occurs, otherwise use condoms
  - Continue PrEP during pregnancy for condomless sex (JC)

HIV and Pregnancy

- Preventing HIV infection in women is the best way to prevent perinatal transmission
- Offer HIV testing to ALL pregnant women
- Treatment is available to nearly eliminate mother to child transmission (MTCT)
- With good medical care and antiretroviral therapy (ART), HIV-infected parents can live long, relatively healthy lives
**Childbearing Women and HIV**

- Approximately one in four people living with HIV infection in the United States is a woman.
- Most new HIV infections in women are from heterosexual contact (84%).
- An estimated 88% of women who are living with HIV are diagnosed, but only 32% have the virus under control.
- 6,000 to 7,000 HIV-positive women deliver annually.
  - Fewer than 200 HIV infected infants are born in the US each year.
  - 40% of HIV-infected infants are born to mothers with unknown status.


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**Mother to Child Transmission in the U.S. Over Time**

<table>
<thead>
<tr>
<th>Year</th>
<th>% Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993: WITS</td>
<td>1%</td>
</tr>
<tr>
<td>1994: PACTG 076</td>
<td>1.5%</td>
</tr>
<tr>
<td>1997: PACTG 185</td>
<td>5.0%</td>
</tr>
<tr>
<td>1999: WITS</td>
<td>3.3%</td>
</tr>
<tr>
<td>2001: PACTG 247</td>
<td>2.0%</td>
</tr>
<tr>
<td>2002: PACTG 316</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Decline due to:
- Enhanced prenatal HIV testing;
- Increase in use of HAART by HIV+women;
- Increase in elective C/S by HIV+ women.

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**Factors Influencing Perinatal Transmission**

- **Maternal Factors**
  - **Viral load**
    - Newly infected?
    - Very high VL ????
    - HIV-1 RNA levels
  - **CD4 lymphocyte count**
  - **Other infections**
    - Hepatitis C
    - CMV
    - BV
    - Genital ulcer
  - **Maternal IVDU**

- **Obstetrical Factors**
  - Length of ruptured membranes/chorioamnionitis
  - Vaginal delivery
  - Invasive procedures

- **Infant Factors**
  - Prematurity
• Determining the **timing** of perinatal HIV infection is of great clinical relevance for implementing cost-effective prophylaxis.

• Recent studies argue that most HIV transmission occurs very late in gestation.

  *Kourtis, Bulterys, Nesheim, Lee. JAMA 2001; 285:709-712*

---

### Perinatal Transmission

<table>
<thead>
<tr>
<th>Breast-feeding populations</th>
<th>Non-breast feeding populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall risk 20-45%</td>
<td>Overall risk 15-30%</td>
</tr>
</tbody>
</table>

Among transmissions:
- In utero: 15-25%
- Intra partum: 35-45%
- Breast feeding: up to 40%

- **Target with all interventions <5%**
- **Target with all interventions <2%**

---

**Mofenson et al NEJM 374:8**
How Important is Maternal Viral Load?

- Maternal HIV-1 RNA level is strongly correlated with risk of transmission
- RNA level near the time of delivery is an important predictor of transmission even among ARV-treated women
- The threshold, below which transmission does not occur, has not been determined

Antiretroviral Therapy in Pregnancy: Protective Benefits to the Infant

- Mechanisms of protection:
  - Reduce maternal plasma viral load by using combination antiretroviral therapy (cART)
    - Reduce infant in utero exposure
  - Reduce genital viral load
    - Reduce infant viral exposure in birth canal
  - Drugs crossing the placenta provide infant pre- and post-exposure prophylaxis

Antiretrovirals in Pregnancy

- Initiate combination ART treatment for mother as soon as possible: pre-conception or during pregnancy
  - TasP: treatment of mother patient to reduce in utero exposure
  - Mother continues lifelong ART after delivery
  - Continue maternal oral regimen during labor
  - If patient’s ART includes ritonavir (NFV) or efavirenz (EFV) give 1 hour post-exposure
  - Oral zidovudine to infant for 4-6 weeks
  - Nevirapine 3 doses in 1st week added if mother had no ART in pregnancy or if maternal HIV RNA >1000
  - some recommend ZDV/3TC/NVP up to 6 weeks for high risk
  - Scheduled Cesarean delivery recommended at 38 weeks if HIV RNA >1000 at 36 weeks
  - IV zidovudine 3 hours prior to surgery if HIV RNA >1000 or no prior maternal ART
  - CYP3A4 interactions may effect methergine/other ergotamines

DHHS Perinatal HIV Guidelines November 2017
DHHS Perinatal ARV Guidelines 7 December 2018
ACOG L&D Management of Women with HIV Infection September 2018
Standards for ART in Pregnancy

- cART starts as soon as possible after diagnosis
  - Include AZT in regimen if possible. Not anymore
  - Women should
    - Continue their ART regimen during pregnancy, provided it is well-tolerated and effective in suppressing viral replication
    - Continue taking their antepartum combination antiretroviral therapy (ART) on schedule as much as possible during labor and before scheduled cesarean delivery
- Add IV AZT during labor? If VL > 1000
- Infant receives 4 weeks of oral AZT, if mother had no ART in pregnancy or maternal HIV RNA > 1000, nevirapine 3 doses in first week
- Women should continue on ART after delivery
  - cART is currently recommended for all HIV-infected individuals to reduce the risk of disease progression and to prevent HIV sexual transmission

Teratogenicity

- Antiretroviral Pregnancy Registry (http://APRegistry.com)
- Inform mothers that drugs are prescribed based upon available safety data from animal toxicity data, registry data, and clinical trials
- Based on multiple studies showing no difference in birth defect rates for 1st trimester exposure vs later ARV exposures, ARV during pregnancy does not increase the risk of birth defects.

Pharmacokinetic Concerns for Antiretrovirals

- Pharmacokinetic considerations
  - Physiologic changes affect drug absorption, distribution, elimination, etc.
  - Prolonged GI transit time
  - Placental transport/compartamentalization
- PKs of NRTI and NNRTIs: non-preg=preg
- PKs of PI and integrase inhibitors: variable
Current Antiretroviral Agents in 7 Classes

**NRTI/NtRTI (8)**
- abacavir (Ziagen) "ABC"
- didanosine (Videx) "ddI"
- emtricitabine (Emtriva) "FTC"
- lamivudine (Epivir) "3TC"
- stavudine (Zerit) "d4T"
- tenofovir DF (Viread) "TDF"
- tenofovir AF (Vemlidy) "TAF"
- zidovudine (Retrovir) "AZT, ZDV"

**NNRTI (5)**
- efavirenz (Sustiva) "EFV"
- nevirapine (Viramune) "NVP"
- doravirine (Pifeltro, Delstrigo) "DOR"
- etravirine (Intelence) "ETR"
- rilpivirine (Edurant) "RPV"

**Integrase strand transfer inhibitor (4)**
- elvitegravir (only in STR) "EVG"
- bictegravir (only in STR) "BIC"
- dolutegravir (Tivicay) "DTG"
- raltegravir (Isentress) "RAL"

**Protease Inhibitors (9)**
- atazanavir (Reyataz) "ATV"
- darunavir (Prezista) "DRV"
- fos-amprenavir (Lexiva/APV) "FAPV"
- indinavir (Crixivan) "IDV"
- nelfinavir (Viracept) "NFV"
- saquinavir "SQV"
- tipranavir (Aptivus) "TPV"
- ritonavir "RTV"

**Fusion Inhibitor (1)**
- enfuvirtide (Fuzeon) "T-20"

**CCR5 Receptor Blocker (1)**
- maraviroc (Selzentry) "MVC"

**Anti-CD4 Antibody (1)**
- ibalizumab-uiyk (Trogarzo) "IBA"

**Pharmacologic Boosters (2)**
- cobicistat (Tybost) "COBI"
- ritonavir (Norvir) "RTV"

---

Recommended ART in Pregnancy

**Dual Nucleoside Backbone**
- Truvada
- Tenofovir DF/emtricitabine
- Epzicom
  - abacavir/lamivudine
  - HLA B5701 negative only

**Alternative nucleoside backbone**
- Combivir: zidovudine/lamivudine
- Alternative NNRTIs: efavirenz or rilpivirine
- Alternative PI:
  - nelfinavir/ritonavir

**Integrase Inhibitor**
- raltegravir
  - 400 mg twice daily
  - Some risk at conception

**Alternative PI**
- atazanavir/ritonavir
  - Once daily
  - ATV 400 mg 2nd/3rd trimester
  - darunavir 600 mg/ritonavir twice daily

**Boosted Protease Inhibitor**
- atazanavir/ritonavir
  - Once daily
  - ATV 400 mg 2nd/3rd trimester
  - darunavir 600 mg/ritonavir twice daily

**CHANGES...**

- Threshold for additional prophylaxis for infants has changed
  - Exposed infants born to women with controlled HIV VL receive 4 weeks of zidovudine (not 6 weeks)

- VL over 1000

- High risk (no meds, newly identified, other infection) consider adding nevirapine
In women who are receiving a cytochrome P450 3A4 enzyme inhibitor such as protease inhibitors (Atazanavir, Lopinavir, Darunavir, Fosamprenavir, Indinavir, etc), methergine should be used only if no alternative treatments for postpartum hemorrhage are available and the need for pharmacologic treatment outweighs the risks.

- If used, methergine should be administered in the lowest effect dose for the shortest possible duration. Misoprostol and carboprost (hemabate) should be first line agents for hemorrhage.

In women who are receiving a CYP3A4 enzyme inducer such as nevirapine, efavirenz, or etravirine, additional uterotonic agents may be needed due to potential for decreased methergine levels and inadequate treatment effect.

Breast Feeding and HIV Infection
**U ≠ U in Breast Feeding**

- Maternal antiretroviral therapy reduces but does not eliminate transmission through breast milk.
  - In low-middle income countries, there is a 15-20% risk of HIV transmission through breast feeding over 2 years.
  - In a study of maternal ART vs infant NVP prophylaxis, there was 0.3% transmission rate at 6 months and 0.6% at 12 months. Transmissions occurred despite maternal virologic control.
- Safe and affordable substitute feeding is available in the US.
- There are few safety data on use of antiretroviral medications during breast feeding.
- Women who decide to breast feed after thorough counseling should be supported with harm reduction interventions:
  - ART in mother with frequent RNA monitoring.
  - Infant prophylaxis for 6 weeks.
  - Weaning at 6 months.

**What if a HIV infected woman wants to breast feed?**

Avoidance of breastfeeding has been the DHHS recommendation for three decades.

**Harm reduction counseling**

- Validate her desire to breastfeed
  - Encourage discussion about her feelings and thoughts well before delivery.
- Seek to understand her motivation
  - Is it social or cultural?
    - Stigma, cultural pressure, and/or awareness of benefits of breastfeeding.
  - Knowing the motives can guide counseling.

Potential Interventions

- Explore alternatives
  - Formula feeding (0% risk of transmission)
  - Banked breast milk
    - Milk banks pasteurize donated human milk and test donor for HIV
- Offer harm reduction
  - After emphasizing formula as optimal, offer exclusive breastfeeding with maternal and/or infant ARV therapy
  - Risk of transmission 0.4-0.8%
  - Flash heating of breast milk inactivates the infectivity of HIV in vitro without losing nutritional value
  - Lactational surrogate
    - Needs to be HIV negative
    - Rule out HIV in infant

Summary

- Incidence of HIV is trending down for women for first time in a decade
- Lowering viral load to undetectable remains a cornerstone of preventing perinatal transmission of HIV
- DHHS guidelines currently call for avoidance of breastfeeding, but as more research becomes available this position may change
- Despite clear guidelines for screening all pregnant patients, there are still missed opportunities for preventing infected babies, making MTCT of HIV unlikely to be a never event
HEPATITIS B & C IN PREGNANCY

Elizabeth J. May, MD, PhD

Elizabeth May, MD, PhD is a board certified academic internist, gastroenterologist and hepatologist currently teaching as Professor of Medicine at Wayne State University School of Medicine. She currently serves as Chair of the Membership and Mentorship Committee for the American Association for the Study of Liver Disease (AASLD). She is a member of the AASLD Diversity and Inclusion Committee. Dr. May is guest co-editor of the AASLD electronic journal “Clinical Liver Disease.” Dr. May initiated and staffs the GI Geriatric Clinic at Rosa Parks Geriatric Clinic. She has served as GI Division Chief at Detroit Receiving Hospital, Mercer School of Medicine, and Morehouse School of Medicine. She has been Associate Chair of Medicine at Morehouse School of Medicine. Her drive to educate continues to reach patients, families, students, trainees and colleagues. Her recent research interests include mentorship of trainees, diagnostic strengths and limitations of lab tests, and hepatitis C treatment.
HBV and HCV infection in Pregnancy

December 9, 2019
Elizabeth J May MD PhD
Professor of Medicine
Wayne State University

Dr. May is Guest Associate Editor of Clinical Liver Disease and otherwise has no relationships or conflicts of interest to declare. Discussion of an FDA non-approved use of a pharmaceutical is likely and will be identified.
HBV and HCV screening during pregnancy

- Universal HBV screening (HBsAg) during pregnancy was implemented from 1994 by CDC.
- Uninfected individuals should receive HBV vaccination during pregnancy. Infection should be referred to a hepatologist to determine if treatment is needed.
- In 2019, AASLD guidelines recommend HCV screening (HCV Ab) for all in pregnancy in light of the opioid epidemic and a rise in women infected with HCV.
- 40-92% with HBV infection are unaware. Cohen, 2011
- 50% of HCV infected individuals do not know. Denniston, 2012

Let’s start with a case...

- Clinic consult for a 25 year old Asian female with newly diagnosed chronic Hepatitis B infection.
  - What do you recommend for family counseling?
    - Parents, partners, children, siblings and household contacts – test, vaccinate, educate, treat, monitor!

Big Picture - HBV

- Viral hepatitis affects mother and baby. Pregnancy can complicate the infection.
- Vertical transmission compromises infant well being and prognosis.
- Prevention by vaccinating mother before or during pregnancy
- Treatment differs in pregnancy
Key Issues

- HBV Transmission
- Viral infection effects on maternal health and fetal health
- Pregnancy effects on the course of viral hepatitis
- Treatment of HBV during pregnancy
- Prevention of mother to child transmission (MTCT)

HBV transmission

- 65 million women of childbearing age are infected with chronic HBV.
- Worldwide, vertical transmission is the most common route. 90% of infants exposed to virus without immunoprophylaxis become chronically infected.
- In low endemic areas (US) horizontal transmission is the most important route.
- HBV is highly contagious via contact with infected blood, fluid, or skin lesions.
- HBV can survive 7 days outside the body and remain capable of transmitting infection.
- 14-60% of chronic HBV infected persons households have resolved HBV infection by serology. 3-20% are infected.
- Since 1982, serology and HBV vaccination of household contacts and partners is recommended. Weinbaum, 2009

Estimated rates of HBV and HCV mother-to-child, sexual and household contact transmission risk Kushner, 2018
Ist prospective study of benefit of immunoprophylaxis (HBIG + vaccine) to 138 infants at 9 mos old

HBV DNA < 10^5 IU/ml

HBV DNA > 10^8 IU/ml

HBV DNA 10^5 – 10^8 IU/ml

HBV treatment during Pregnancy

- Goals are to maintain maternal liver function and prevent fetal infection.
- Severe maternal disease may require antiviral therapy throughout pregnancy
- If HBV DNA >= 200,000 IU/ml, guidelines support beginning treatment with nucleos(t)ides at week 26-28 gestation until delivery -30 days post partum.
- Lamivudine, telbivudine, and tenofovir are options with no apparent teratogenicity.
- Monitor LFTs, HBeAg status, and HBV DNA during gestation.
Tenoforvir to prevent Hepatitis B transmission to mothers with high viral load Pan, CQ NEJM 2016

Guidelines for prevention of HBV MTCT

<table>
<thead>
<tr>
<th>Year update</th>
<th>Organization</th>
<th>Drug of choice</th>
<th>Time to initiate</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TDF, LdT</td>
<td>28-32</td>
<td>&gt;10^6</td>
</tr>
<tr>
<td>2015</td>
<td>APASL</td>
<td>TDF, LdT</td>
<td>28-32</td>
<td>&gt;2x10^5</td>
</tr>
<tr>
<td>2015</td>
<td>AASLD</td>
<td>TDF, LAM, LdT</td>
<td>28-32</td>
<td>&gt;2x10^5</td>
</tr>
<tr>
<td>2017</td>
<td>EASL</td>
<td>TDF(preferred)</td>
<td>24-26</td>
<td>&gt;2x10^5</td>
</tr>
</tbody>
</table>

MTCT mother to child transmission
TDF, tenofovir disoproxil fumarate.
LdT, telbivudine. LAM, lamivudine
HBV Effects on maternal health

- Acute HBV can cause fatigue, nausea, vomiting, abdominal pain, and jaundice.
- Acute infection outcome is without death or teratogenicity.
- HBV cirrhosis/pregnancy is rare. If portal hypertension is present, risk of decompensation, variceal bleeding, and death.
  - EGD is recommended in second trimester to assess/treat varices or Beta-blocker to reduce risk of variceal rupture.

HBV Effects on fetal health

- Infection early in pregnancy has a 10% MTCT risk; Third trimester infection, it is 60%.
- Acute infection during pregnancy can lead to low birth weight and prematurity.
- Threatened preterm labor is risk for changing low (HBV DNA< 200,000 IU/ml) to high risk for MTCT. Pan CG 2012

Pregnancy Effects on the Natural History of chronic HBV Infection

- 6-14% risk of HBV flares during pregnancy.
- 10-50% flare after delivery
- In absence of fibrosis and hepatitis delta co-infection, flares are mild and self-limited.
- ALT monitoring for 6 months after delivery or stopping antiviral medication during pregnancy is recommended.
- In one study gestational DM, antepartum hemorrhage and threatened preterm delivery were associated with chronic HBV infection.
- Chronic HBV and pregnancy with cirrhosis are associated with increased maternal and fetal mortality so co-management with high risk obstetric or maternal fetal medicine specialist.
Pregnancy associated hepatitis B flares

<table>
<thead>
<tr>
<th>Author-year</th>
<th>Country</th>
<th>No. Pregnancies</th>
<th>ALT Flare definition</th>
<th>Flare Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ter Borg, 2008</td>
<td>Netherlands</td>
<td>38</td>
<td>baseline</td>
<td>45% postpartum</td>
</tr>
<tr>
<td>Nguyen, 2014</td>
<td>Australia</td>
<td>151</td>
<td>5xULN</td>
<td>32% postpartum</td>
</tr>
<tr>
<td>Nguyen, 2014</td>
<td>Australia</td>
<td>151</td>
<td>4x daily/AVT cessation</td>
<td>45% postpartum</td>
</tr>
<tr>
<td>Nguyen, 2014</td>
<td>Australia</td>
<td>151</td>
<td>3x baseline/AVT cessation</td>
<td>45% postpartum</td>
</tr>
<tr>
<td>Nguyen, 2014</td>
<td>Australia</td>
<td>151</td>
<td>1x untreated</td>
<td>29% postpartum</td>
</tr>
<tr>
<td>Giles, 2015</td>
<td>Australia</td>
<td>136</td>
<td>3xULN</td>
<td>22% postpartum</td>
</tr>
<tr>
<td>Chang, 2016</td>
<td>US</td>
<td>113</td>
<td>5xULN or 3x baseline</td>
<td>11% during preg, 14% postpartum</td>
</tr>
<tr>
<td>Kushner, 2017</td>
<td>US</td>
<td>310</td>
<td>2xULN</td>
<td>14% during preg, 16% postpartum</td>
</tr>
<tr>
<td>Liu, 2017</td>
<td>China</td>
<td>1097</td>
<td>2xULN</td>
<td>1.9% 1st trimester, 2.1% at delivery, 9.8% 1 month postpartum</td>
</tr>
</tbody>
</table>

AVT: antiviral therapy, ULN: upper limit of normal

FAQs HBV and pregnancy

- Does amniocentesis increase the risk of infection transfer?
  - Two studies with 27 and 45 patients concluded no increase. Yet, another study saw 2.3 odds ratio increase risk of infection when HBV DNA > 7 log copies/ml. Risks vs benefits discussion
- Is it safe to breastfeed?
  - Yes, low levels of antivirals found in breast milk
- Is C-section beneficial?
  - No, due to insufficient data

HCV Big Picture

- 29,000 HCV infected women gave birth each year in the US, 2011-2014
- 75 million people worldwide are HCV infection estimates. In US, a 1.4:1 Female: Male ratio (Esmaeilli 2017) is reported.
- 3.6% prevalence in pregnancy some US cohorts although 2.4% vertical transmission rates prevail.
- HCV RNA titer is lower than HBV DNA in body fluids

Dynamics of HCV Prevalence in US

Hepatitis C Prevalence

- New HCV Infections
- 15%
- Spontaneous Clearance
- Cirrhosis-HCC
- Death

Treatment Goals

- Cure
- Remission
- SVR
- Survival

Contraindications to treatment include:
- Liver failure
- HCC
- Hepatitis C superinfection
- Recent hepatic decompensation
- Recent esophageal varices
- Active alcohol use or drug abuse
- Severe psychiatric illness
- Poor nutritional status

Success rates:
- SVR rates:
  - Interferon plus ribavirin: 40-50%
  - Peginterferon plus ribavirin: 50-60%
- Cure rates:
  - Interferon plus ribavirin: 20-30%
  - Peginterferon plus ribavirin: 30-40%
HCV Impact on maternal and infant health

- HCV MTCT appears to be 5-15% and is the leading cause of HCV infection in children.
- Up to 50% MTCT occurs prior to last month of pregnancy, the rest occurs in last month of pregnancy or delivery. No prenatal or interpartum care intervention (delivery mode) lowers risk.
- Progression to chronic infection 3-5%.
- HCV infection in pregnancy with pruritus or jaundice, evaluate for ICP (check LFTs, and bile acids).
- HCV and ICP are associated and together increase adverse outcomes. Wijarnpreecha 2017 Refer such patients to maternal fetal specialists.
- HCV infection in pregnancy with cirrhosis warrants counseling for increased risk of adverse events and perinatal outcomes and care coordination as high risk.

HCV Impact on Pregnancy and perinatal outcome

- Preterm delivery, low birth weight and congenital anomalies have been reported, but data confounded by comorbidities.
- Cirrhosis and pregnancy increase risk for preeclampsia, c-section, hemorrhage, and death.
- Preterm delivery, low birth weight and death are neonatal outcomes with cirrhosis. Tan 2008

Pregnancy impact on HCV infection

- No harmful impact is reported. ALT levels decrease in second and third trimesters and return to baseline after delivery.
- Studies disagree whether pregnancy decreases or increases liver fibrosis. (Resti 1998, Fontaine 2000)
FAQs HCV and pregnancy

- HCV treatment should not be offered during pregnancy
  - CROI 2019: 8/8 HCV infected pregnant women achieved SVR after 12 weeks of ledipasvir/sofosbuvir beg at weeks 28 (Leutkemeyer, 2019)
  - No postpartum HCV flares reported. Reassess women after delivery for up to 10% -25% have spontaneous clearance which is associated with a favorable IL28B allele. (CC) Hashem M (2017)
  - Breastfeeding is safe in the absence of cracked, damaged, or bleeding nipples or HIV co-infection.

Key Points

<table>
<thead>
<tr>
<th></th>
<th>HBV in pregnancy</th>
<th>HCV in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal Screening</td>
<td>Yes, since 1984</td>
<td>Perhaps, since 2019</td>
</tr>
<tr>
<td>Diagnosis Self-awareness</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>MTCT Rate</td>
<td>30-60%</td>
<td>5-15%</td>
</tr>
<tr>
<td>Treatment</td>
<td>DNA&gt;200,000 IU/ml Week 26-28 to term</td>
<td>Not yet</td>
</tr>
<tr>
<td>Flare During Pregnancy</td>
<td>6-14%</td>
<td>No</td>
</tr>
<tr>
<td>Perinatal Outcome</td>
<td>Low birth weight Preterm delivery</td>
<td>Low birth weight Preterm delivery Demise</td>
</tr>
</tbody>
</table>
Suresh B. Boppana, MD

Suresh B. Boppana, MD is a Professor of Pediatrics and Microbiology and Hugh Dillon MD Endowed Professor in Pediatric Infectious Diseases at the University of Alabama at Birmingham. He has been studying the natural history and pathogenesis of maternal and congenital cytomegalovirus (CMV) infection for over 25 years. Suresh’s work challenged the dogma by documenting the importance of non-primary maternal infections in the overall disease burden from congenital CMV infection. His research has also documented the impact of congenital CMV in highly seropositive settings including developing countries. As the co-PI of large multicenter study newborn CMV screening study, he reported on low sensitivity of dried blood spot PCR assay and the utility of a highly sensitive and specific saliva real-time PCR assay for newborn CMV screening. His current work focuses on understanding the immune correlates protection using the acquisition of CMV infection using the human breast milk transmission setting as a model. He is also the co-medical director of the Antimicrobial Stewardship Program at the Children’s of Alabama since 2016 and is committed to improve patient outcomes by encouraging optimal antimicrobial therapy and reduce the emergence of resistant organisms.
OVERVIEW OF TORCH INFECTIONS

Karen E. Johnson, MD

Karen E. Johnson, MD is an Associate Professor of Pediatrics in the Section of Neonatology and Associate Dean of Admissions at Baylor College of Medicine. She is an attending neonatologist and program director of the Perinatal Pediatric Advanced Care Team at Texas Children’s Hospital Newborn Center in Houston, Texas. Dr. Johnson earned her doctor of medicine degree from Baylor College of Medicine, where she continued her postdoctoral training, completing her residency in pediatrics and fellowship training in neonatal-perinatal medicine. Dr. Johnson is board certified in both neonatal-perinatal medicine and palliative care. Dr. Johnson is a dedicated educator and clinician who enjoys the challenges of academic medicine and everyday patient care. She is committed to improving the quality of life for patients with chronic or life-threatening illness and ensuring the future of healthcare by teaching and mentoring the next generation of medical professionals.
OVERVIEW OF TORCH INFECTIONS
Wayne Day
December 2019
Karen E. Johnson, MD

OBJECTIVES
1) REVIEW THE HISTORY OF TORCH INFECTIONS IN PERINATAL MEDICINE
2) RECOGNIZE CLINICAL MANIFESTATIONS
3) DESCRIBE DIAGNOSTIC/Therapeutic Associations
TORCH INFECTIONS

Toxoplasma gondii (parasite)
- 400-4,000 cases each year in US; ~200,000 cases worldwide annually
- Risks: eating uncooked meat/unwashed produce/touching contaminated cat feces
- No maternal screening in US
- 70-90% of newborns are asymptomatic at birth
- "Classic triad": chorioretinitis, hydrocephalus, intracranial calcifications

SYPHILIS - Treponema pallidum (spirochete)
- 628 reported cases in the US (2016)
- Highest rates: Southern states/minority populations
- Primary/secondary/latent categories
- Newborns typically asymptomatic
- Hydrops, premature birth, stillbirth for severe cases
- Universal screening (RPR/VDRL)

Leeper, C; Lutzkanin A; Infections During Pregnancy; Primary Care: Clinics in Office Practice; September 2018 Vol 45, Issue 3, pages 567-586

TORCH INFECTIONS

- Newborn symptoms: multi organ
  - "snuffles", rash on palms and soles, bone abnormalities, abnormal CBC, HSM
- IV aqueous PCN primary therapy x 10 days
- Follow-up imperative
**TORCH INFECTIONS**

**Rubella (single-stranded RNA virus)**
- Congenital Rubella Syndrome (CRS) is rare
- US National Rubella Registry 5-6 cases/year
- More immigrant/migrant/anti-vaccine populations
- Maternal screening (Rubella immune)

**Congenital Rubella Syndrome (CRS)**
- "Classic" symptoms: IUGR, intracranial calcifications, cataracts, "blueberry muffin" rash, abnormal CBC, HSM
- Congenital Heart Defects: PDA, pulmonary stenosis
- Sensorineural hearing loss
TORCH INFECTIONS

C-cytomegalovirus (DNA virus)
- Most common congenital infection (~2% of live births)
- Geography/SES status and work category 'risk factors'
- 1st trimester infections more severe fetal/NB disease
- No routine screening

References:
McAuley, J; Congenital Toxoplasmosis; Journal of Pediatric Infectious Diseases Society, Vol. 3, Suppl 1, pp S30-35; June 2014

TORCH INFECTIONS

C-Cytomegalovirus
- 90% cause no symptoms
- 10% microcephaly, thrombocytopenia, HSM, IUGR
- Intracranial calcifications
- 30% with severe CMV die
- Neurosensory hearing loss
- World-wide-most common cause non-hereditary hearing loss
- Valganciclovir in severe cases
TORCH INFECTIONS

**H-herpes simplex virus**
- 30-60% seropositive women receiving OB care
- HSV-2 causes 70% neonatal cases
- 90% perinatally transmitted – vaginal delivery

3 distinct NB manifestations:
1) Disseminated infection (25%)
2) Skin, eye, mouth (SEM) infection (45%)
3) CNS (30%)
   - Acyclovir effective therapy

TORCH TOO??
1) VARICELLA-ZOSTER
2) PARVOVIRUS B19
3) HIV
4) ZIKA
‘EXTENDED’ TORCH INFECTIONS

ZIKA (single-stranded RNA flavivirus)
1) severe microcephaly
2) decreased brain tissue, subcortical calcifications
3) damage to the back of the eye-macular scarring/focal retinal pigmentary mottling
4) Congenital contractures (clubfoot or arthrogryposis)
5) hypertonia restricting body movement soon after birth

Varicella-zoster virus
- Low pregnancy incidence
- Newborn symptoms (IUGR, skin lesions or scarring in a dermatomal distribution; chorioretinitis; hypoplastic limbs)

Parovirus B19
- Spontaneous abortion, stillbirth and hydrops fetalis associated
- 1-2% new infections during pregnancy

Leeper C, Lutzkanin A; Infections During Pregnancy; Primary Care Clinics in Office Practice; Sept 2018 Vol 45, Issue 3, p567-586
Human immunodeficiency virus (HIV)

- Universal screening
- In US ~ 8700 HIV + women give birth yearly
- Antenatal antiretroviral (ARV) rx decrease vertical transmission
- Newborns asymptomatic (empiric rx with ARVs and serial virologic tests 1st 6 months)
- Zidovudine standard therapy

"TORCH titers" costly, not effective/poor diagnostic yield

Maternal history/fetal findings and newborn exam-suspected specific pathogen should direct tests/therapies
TORCH INFECTIONS

CLINICAL SUSPICION IN NB
- Hydrops fetalis
- Microcephaly
- Seizures
- Cataract
- Hearing loss
- Congenital heart disease
- Hepatosplenomegaly
- Jaundice
- Rash
- Thrombocytopenia

INITIAL EVALUATION
- Review of maternal history (evidence of rubella immunity, syphilis serology, history of herpes simplex virus [HSV], exposure to cats, etc)
- Assessment of physical stigmata consistent with various intrauterine infections
- Complete blood count and platelet count
- Liver function tests (particularly important in HSV infection)
- Radiographs of long bones
- Ophthalmologic evaluation
- Audiologic evaluation
- Neuroimaging (MRI)
- Lumbar puncture

AAP Red Book 2018-2021
- UpToDate: Overview of TORCH Infections
- CDC.gov
- Infections During Pregnancy; Leeper and Lutzkanin Sept 2018 Primary Care Clinics in Office Practice
TORCH INFECTIONS

thanks
KEYNOTE ADDRESS

LETHAL MATERNAL INFECTIONS: GROUP A STREPTOCOCCUS WITH NECROSIS, NECROTIZING FASCIITIS

David A. Eschenbach, MD

David A. Eschenbach, MD completed an Obstetrics and Gynecology Residency at the University of Washington and an Infectious Diseases Fellowship at the same institution. His area of expertise is infectious diseases of the genital tract. He has over 200 peer-reviewed publications, virtually all on infectious diseases of the genital tract. He was Chair of Obstetrics and Gynecology at the University of Washington for 17 years, and now is a Professor in the Department.
OBJECTIVES

Treatment of Serious Maternal Infections

You will be able to:
- review the pathophysiology and treatment of sepsis
- identify the toxin-producing bacteria least likely to respond to antibiotics
- know the clinical features of a serious infection
- know all treatment options for a serious infection
**CAUSES OF MATERNAL DEATH**

1991–96

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>33%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16%</td>
</tr>
<tr>
<td>Early pregnancy</td>
<td>13%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>10%</td>
</tr>
<tr>
<td>Amniotic fluid embolism</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td><strong>9%</strong></td>
</tr>
<tr>
<td>Anesthesia</td>
<td>4%</td>
</tr>
<tr>
<td>Other direct</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>254</strong></td>
</tr>
</tbody>
</table>

**PATHOGENESIS OF INFECTION**

- Presence of pathogen
  - Depends on other flora
  - Concentration of pathogen
- Invasion of pathogen
  - Break in barrier
  - Invasive property of bacteria
- Infection
  - Pathogenicity of bacteria
  - Immune response
  - Genetic polymorphism
  - Exogenous medication
  - Endogenous disease

**PROMPT PROTECTIVE TISSUE RESPONSE**

Bacterial invasion

Recognition by innate immunity

TISSUE RESPONSES
Fragmented Communication Between Immune Cells

Genetically identical bacteria can behave in radically different ways

Survival means diversity for bacteria

- Metabolism
- Motility
- Growth
- Biofilm formation
- Toxin production

Host Response in Severe Sepsis
LOCAL TISSUE RESPONSE

- Blood vessel dilation
- Fluid leakage/thrombin formation
- Microcirculation damage

ANAEROBIC METABOLISM
LACTIC ACIDOSIS

DEFINITIONS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Presence (probable or documented) of infection, with systemic manifestations of infection</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>Sepsis + sepsis-induced organ dysfunction or tissue hypoperfusion</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>Sepsis-induced hypotension, persisting despite adequate fluid resuscitation</td>
</tr>
<tr>
<td>Sepsis-Induced Tissue Hypoperfusion</td>
<td>Infection-induced hypotension, elevated lactate or oliguria</td>
</tr>
</tbody>
</table>
### Diagnostic Criteria for Sepsis

**Infection (documented or suspected) + the following**

**General**
- Fever >38.3°C
- Hypothermia <36°C
- Heart rate >90
- Tachypnea
- Altered mental status
- Significant edema
- Hyperglycemia >140 mg/dl

**Inflammatory**
- Leukocytosis >12,000
- Leukopenia <4,000
- >10% immature cells
- Plasma CRP >2X
- Plasma procalcitonin 2X normal

**Hemodynamic**
- Arterial pressure <90 mm, MAP <70 mm or SBP drop <40 mm

**Organ Failure**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Shock, Lactic acidosis, Coagulation defect</td>
</tr>
<tr>
<td>Lung</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td>Renal</td>
<td>Oliguria</td>
</tr>
<tr>
<td>CNS</td>
<td>Dysfunction</td>
</tr>
</tbody>
</table>

Risk of death increases 15-20% with each additional organ failure

### Diagnostic Criteria for Organ Dysfunction

**Organ Dysfunction**
- Arterial hypoxemia PaO₂ <300
- Acute oliguria <0.5 ml/kg/hr for 2 hrs
- Creatinine rise >0.5 mg/dl
- Coagulation INR >1.5, aPTT >60s
- Thrombocytopenia <100,000
- Hyperbilirubinemia >4 mg/dl
- Ileus

**Tissue Perfusion**
- Hyperlactatemia >1 mmol/L
- Decreased capillary filling or mottling
CELLULAR METABOLISM / SEVERE SEPSIS

- **Perfusion**
- **Glycolysis**
  - Decreased delivery of oxygen
  - Decreased anaerobic metabolism
- **Metabolic acidosis**
- **Lactate**
**TREATMENT GOALS**
- Treat nidus
- Support organs
- Block toxic mediators

**EARLY POSTPARTUM INFECTION**
*Exacerbation of Preexisting Infection*
- Amniotic fluid infection
  - Uterine and peritoneal
- Urinary tract infection
- Abscess rupture with delivery
**CAUSES OF EARLY POSTPARTUM INFECTION**

- Exacerbation of preexisting infection
- Rapidly developing
  - Soft tissue infection
  - Wound infection
- Intravenous line infection
- Noninfectious causes simulating bacterial infection

**EARLY POSTPARTUM INFECTION**

Rapidly developing soft tissue infection:
- Group A *Streptococcus*
- *Clostridium perfringens*
- Other Clostridia
- Other organisms (*rare*)

**CASES RAPIDLY DEVELOPING INFECTION**

- Myonecrosis
  - *Clostridium perfringens*
  - Other Clostridia, *C. sordellii*
- Cellulitis from toxin-producing organisms
  - *C. sordellii*
  - Other organisms unusual
- Necrotizing fasciitis
- Abscess formation
  - Gram negative aerobic/anaerobic
UNUSUAL SIGNS

Indicating serious infection
Requiring surgical removal

- Septic shock
- Adult respiratory distress syndrome (ARDS)
- Disseminated intravascular coagulation (DIC)
- Hemolysis
- ↑ Area of cellulitis
- Necrosis of tissue

CHANCE MEETING OF TWO UNRELATED EVENTS

DAILY
- 28,000 commercial airline flights in US
- Several thousand flocks of geese fly

DAILY
- Several thousand people develop Group A Streptococcal (GAS) sore throat
- Several pregnant women are exposed to GAS

DAILY
- GAS in the Netherlands/100,000 deliveries:
  — Sepsis 21
  — GAS Sepsis 7
  — GAS Mortality 0.3

January 16, 2009

Occasionally, two unrelated events may collide
Captain Chesley Sullenberger, Pilot

- 31 years experience
- 19,000 air hours
- Practiced water landings

How well did we do with less practice?

Experience + Practice

Case 34 yo prior healthy para 2

Hx: • Delivered 9 days before
  • Family visiting from Florida with sore throats

Admitted to OSH: • 3 days of pain,
  1 day of altered mental status
  • BP 70/??

Diagnosis: Septic Shock

Treatment: • Put on pressors
  • Intubated

Labs: • Blood and uterine culture—GAS

Case 1

T 38.6°C  BP 90/40  P 132
  • Arm swollen with necrotic areas
  • Uterus palpated in abdomen

Diagnosis: GAS Toxic Shock Syndrome
  • Acute Respiratory Insufficiency (Distress)
  • Coagulopathy (INR 1.8)
  • Liver dysfunction (GOT 132)
Case #1

0735 Debridement of hand/arm for necrotizing fasciitis
0935 Vaginal culture
1800 Abdominal CT showing gas in uterine wall
2111 - TAH (fascia only closed)
- Filmy peritoneal adhesions
- Cloudy ascites, 4+ WBCs, 3+ GPC
- Pale boggy uterus with visible areas of pus
- Enlarged liver

Day 2 Arm debrided, off pressors
Day 3 Extubated
Day 11 Arm inspected, wound vac on abd changed

**LAB VALUES BY HOSPITAL DAY**

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Hct</th>
<th>WBCs</th>
<th>Platelets</th>
<th>INR</th>
<th>GOT</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0135</td>
<td>Arm surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1441</td>
<td>15125</td>
<td>12.8</td>
<td>43</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1850</td>
<td>24 12.7</td>
<td>37</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2111</td>
<td>TAH</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>0030</td>
<td>18.9</td>
<td>58</td>
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<td>0.88</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0312</td>
<td>27 37.6</td>
<td>58</td>
<td>1.4</td>
<td>101.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1546</td>
<td>27 30.6</td>
<td>63</td>
<td>2.2</td>
<td>1.08</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>28</td>
<td>26 19.5</td>
<td>142</td>
<td>2.5</td>
<td>0.70</td>
<td></td>
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<tr>
<td>33</td>
<td>19 216</td>
<td>0.70</td>
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<tr>
<td>32</td>
<td>16 340</td>
<td>216</td>
<td>0.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>14 410</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT OF RAPIDLY DEVELOPING SOFT TISSUE INFECTION

- **Antibiotic coverage**
  - Aminoglycoside or 1st generation cephalosporin
  - Clindamycin, imipenem or metronidazole
  - Penicillin or ampicillin

- **Surgical**
  - Surgical exploration usually required
  - Must prove surgery not necessary

A 35-week screening culture for GBS recovers Group A streptococci

What is the most reasonable response?

### GROUP A STREPTOCOCCUS (GAS)

**Vaginal Culture**
- Ignore because GAS infrequently causes neonatal sepsis
- Treat with cephalosporin until delivery
- Treat with penicillin for 1 week and inquire about family members with a sore throat

### NECROTIZING FASCIITIS

**Skin not primarily infected**
- Initially, only edema and erythema present
- Vesicles and bullae form later
- Eventually, skin becomes gangrenous

**Layers Involved**
- Two layers of superficial fascia
  - Superficial layer (Camper's fascia)
  - Deep layer (Scarpa's fascia)
- Deep fascia and muscle not involved
NECROTIZING FASCIITIS

Clinical Features

- Progressive local erythema and edema, despite appropriate antibiotic therapy
- Septic shock in patient with cellulitis
- Marked systemic signs:
  - Fever (temperature may be normal)
  - Prostration

NECROTIZING FASCIITIS

Laboratory Features

- Anemia (may be masked by hemoconcentration)
- Marked leukocytosis (often 20,000–75,000)
- Hypocalcemia
- Hypotension
- Disseminated intravascular coagulopathy (DIC)

NECROTIZING FASCIITIS

Diagnosis

- Immediate wound exploration under anesthesia
- Findings:
  - Exudate thin and watery
  - Pus not present
  - Gray tissue, which can be dissected without bleeding
- Frozen tissue diagnosis may be useful
NECROTIZING FASCIITIS

**Therapy**
- Immediate debridement of necrotic tissue
- Survival rate only 50%:
  - Less with shock
  - Less with Clostridia
- Wide spectrum antibiotic therapy
  - However, survival rate low when antibiotics used alone without surgery
- Multiple debridements often required

NECROTIZING FASCIITIS

**Microorganisms**
- Non-hemolytic Strep + Staphylococci
- Mixed Aerobic/Anaerobic Bact + Clostridia
- Group A ß-hemolytic Strep + Anaerobes
13.5 WEEK PREGNANCY

Hx: 4 prior visits (clinic and ER) for bleeding, abd pain
D&C
Hyst, pressors stopped
Dx Made
Endometritis
SEPTIC ABORTION

13.5 WEEK PREGNANCY

Hx: 4 prior visits (clinic and ER) for bleeding, abd pain
D&C
Hyst, pressors stopped
Dx Made
Endometritis
SEPTIC ABORTION

Cardinal principle of seriously ill care
COMMUNICATION
Call Senior Attending

COMMUNICATION

allowed solving of 15-year-old HIV puzzle in 10 days by gamers using Foldit
**References**

- Severe Sepsis and Septic Shock
  

  

- The Acute Respiratory Distress Syndrome
  
  Ware LB, Mattay MA. NEJM 2000;42:1334–1349.

- Disseminated Intravascular Coagulation
  

- Acute Renal Failure and Sepsis
  

- Severe Sepsis and Septic Shock in Pregnancy
  

**EARLY POSTPARTUM INFECTION**

- Rapidly developing infection:
  - Group A streptococci cellulitis
  - Toxic shock syndrome
  - Necrotizing fasciitis
COMMON MANIFESTATIONS
Severe Postpartum Infection

PHYSICAL EXAM
• Anxiety
• Disorientation
• Prostration
• Severe tenderness
• Unusual temperature elevation (>39°C)
• Cardiac failure

LABORATORY EXAM
• Marked leukocytosis
  (≥25,000)
• Marked leukopenia
  (<1,000)
• Hemoconcentration
• Hematocrit >45% or <20%
• Low urinary output
  (<20 ml/hr)

RAPIDLY DEVELOPING SOFT TISSUE INFECTION

Close scrutiny must immediately follow:
- Organism
- Source of infection
- Possibility of surgical removal

Case #3

E. coli-CAUSED SEPTIC SHOCK

- 27 yo G3P2 at 18 wks gestation
- One-day fever with abdominal cramps
- Arrived in ER with BP of 80/40
- Diagnosis of septic shock
  - What cultures are obtained?
  - What is initial treatment?
**E. coli-CAUSED SEPTIC SHOCK**

Transferred to UWMC

**Delivered in ER:**
- Drained infection site

**Septic Shock Rx:**
- BP 80–90/50
  - Fluid
  - Antibiotics
  - Activated Protein C

**Heart Failure:**
- Ejection fraction 25%
  - Global dysfunction

**Renal Failure:**
- Anuric

---

**E. coli SEPTIC SHOCK**

<table>
<thead>
<tr>
<th>Date</th>
<th>4/3</th>
<th>4/4</th>
<th>4/5</th>
<th>4/6</th>
<th>4/7</th>
<th>4/8</th>
<th>4/10</th>
<th>4/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1O2</td>
<td>50</td>
<td>50</td>
<td>70</td>
<td>100</td>
<td>70</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2</td>
<td>88</td>
<td>68</td>
<td>63</td>
<td>68</td>
<td>84</td>
<td>104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO2</td>
<td>38</td>
<td>36</td>
<td>42</td>
<td>45</td>
<td>41</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Clear</td>
<td>Clear</td>
<td>Infl</td>
<td>Infl</td>
<td>Infl</td>
<td>Infl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DIC** (Disseminated Intravascular Coagulation)

<table>
<thead>
<tr>
<th></th>
<th>4/3</th>
<th>4/4</th>
<th>4/5</th>
<th>4/6</th>
<th>4/7</th>
<th>4/8</th>
<th>4/10</th>
<th>4/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs</td>
<td>25</td>
<td>29</td>
<td>26</td>
<td>45</td>
<td>51</td>
<td>55</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>250</td>
<td>39</td>
<td>30</td>
<td>37</td>
<td>55</td>
<td>94</td>
<td>167</td>
<td></td>
</tr>
</tbody>
</table>

**Additional therapeutic choice?**

---

**E. coli SEPTIC SHOCK**

Treatment of tissue contributing to ARDS and DIC:

- Continue activated protein C
- Surgical removal
- Continued antibiotic
### E. coli SEPTIC SHOCK

**Surgical Removal of Tissue in Complicated Septic Shock**

#### Indicated
- Necrotic tissue in complicated septic shock
- Uterus
- Abdomen
- Necrotizing fasciitis

#### Not indicated
- Pyelonephritis
- Toxic Shock Syndrome
MATERNAL SEPSIS: DIAGNOSIS AND MANAGEMENT

Muhammad Jaffer, MD

Muhammad Jaffer, MD is Program Director of the Anesthesiology Residency program in the Department of Anesthesiology, with subspecialty training in Anesthesiology and Trauma Critical Care. Dr. Jaffar earned his Medical Degree from the Universidad Technologica de Santiago (UTESA), Santo Domingo, Dominican Republic. He completed his Anesthesiology residency at Maimonides Medical Center in Brooklyn, New York and a Critical Care fellowship at the Cleveland Clinic Foundation in Cleveland, Ohio. Dr. Jaffar is board certified in both Anesthesiology and Critical Care. He joined University of Arkansas Medical Center (UAMS), as an Assistant Professor of Anesthesiology and Critical Care in 1998 and in 2008 was promoted to Professor of Anesthesiology. Dr. Jaffar joined the Detroit Medical Center, Wayne State University in Detroit, MI in November 2017 as Program Director of the Anesthesiology Residency Program. He holds the rank of Professor of Anesthesiology, Wayne State University. He is a Fellow of the American College of Critical Care Medicine, the American Society of Anesthesiologists, and the American College of Chest Physicians. His major interests are in graduate medical education (GME), Inter-professional education (IPE), Quality, patient safety and patient centered care. You can contact Dr. Jaffar at 313.745.7233.
INTRODUCTION

SEPSIS

Major cause of morbidity and mortality worldwide

In USA
- Leading cause of death in noncoronary ICU
- 18th leading cause of death overall
- More than 750,000 cases of severe sepsis in the U.S. annually

Sepsis occurs in just 10% of U.S. hospital patients, but it contributes to as many as half of all hospital deaths

In the U.S., more than 500 patients die of severe sepsis daily

What is Sepsis and Septic Shock?

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening organ dysfunction caused by a dysregulated host response to infection</td>
<td>Severe sepsis is sepsis (known or suspected infection with 4 or more manifestations of sepsis) along with sepsis-related tissue hypoperfusion or organ dysfunction</td>
<td>A subset of sepsis in the underlying circulatory and cellular/metabolic abnormalities profound enough to substantially increase mortality</td>
</tr>
</tbody>
</table>
Sepsis related illnesses were the most expensive conditions treated in US hospitals in 2013.
• 20.3 billion dollars
• Cost of care is increasing by 6 billion dollars every year.

Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period.
Between 250,000 – 400,000 Patients are dying in USA secondary to medical errors

Most deaths in patients with severe Sepsis and Septic Shock are attributed to patients co-morbid conditions

Some are due to preventable medical errors which include:
- Delay in recognition of infection
- Delayed Broad Spectrum Antibiotics
- Inappropriate antibiotics selection
- Delayed Source control
- Hospital acquired infections (MRSA, SSI BIs)
- Delayed or under treatment of shock (Early fluid bolus for hypotension and early use of vasopressors)
- Procedural complications

**Incidences**

Severe maternal age
- Obesity and Diabetes
- Placental abruption
- Placental abnormalities
- Assisted Reproductive Technology (ART)
- Emerging Infectious Diseases


Between 250,000 – 400,000 Patients are dying in USA secondary to medical errors

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**FACTS**

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- Delayed Broad Spectrum Antibiotics
- Inappropriate antibiotics selection
- Delayed Source control
- Hospital acquired infections (MRSA, SSI BIs)
- Delayed or under treatment of shock (Early fluid bolus for hypotension and early use of vasopressors)
- Procedural complications
Signs and Symptoms of Sepsis and Septic Shock

- Fever, chills and rigors
- New onset of anxiety, confusion and delirium
- Acute hypoxemia with difficulty of breathing
- New onset of Fatigue and Malaise
- Unexplained nausea and vomiting
- Skin mottling and poor capillary refill

Common Infections in Obstetrics

- Postpartum endometritis
  - Cesarean delivery: 15-87 %
  - Vaginal delivery: 1-4 %
- Lower tract UTI: 1-4 %
- Septic abortion: 1-2 %
- Pyelonephritis: 1-2 %
- Chorioamnionitis: 0.5 - 1 %
- Necrotizing fasciitis: < 1 %
- Toxic shock syndrome: < 1 %

Maternal Morbidity During Hospitalization with SEPSIS

- 1680 women with severe sepsis
  - E. Coli: 27%
  - Staphylococcus: 22%
  - Streptococcus: 20%
  - Gram Negative: 19%
  - Pneumococcal: 4%
  - Pseudomonas: 2.4%

*Creasy, Resnick and Iams 2010*

*Bauer et al. Anesth Analg 2013*
Early Recognition
• Implementation of Sepsis Screening tool
• OB-RRT

Early Interventions
• Three Hour Bundle
• Six Hour Bundle

Improved Outcomes
• Improved morbidity and mortality

Early Recognition and Screening for sepsis on Obstetric Ward

Early

Prevent
• Prevent progression to organ failure
• Prevent Severe sepsis and septic shock

Evaluate
• Evaluate at regular interval
• Timely and safe disposition

Prevent

Early Recognition
• Timely Intervention
• Implement 3 H and 6H care bundle
Inpatient Sepsis

Vital Signs

Frequency of vital signs
Why we document vital signs?
Most of the patients who deteriorate in hospitals or skilled nursing facilities had signs and symptoms of deterioration hours before

Early warning systems (MEWS, EWS)
Sepsis screen
Presence of two or more SIRS criteria and a suspected source of infection

SEPSIS

There are many scoring systems available but none have been validated for pregnant women
### Obstetric Early Warning Score Escalation Protocol

<table>
<thead>
<tr>
<th>Screening</th>
<th>Multi-Screening for Fever</th>
<th>Paediatric Multi-Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS (Systemic Inflammatory Response Syndrome)</td>
<td>- Presence of any 2 of the following features:</td>
<td>- Presence of any 2 of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>- Temperature &lt; 36 or &gt; 38.3 ℃</td>
<td>- Temperature &lt; 36 or &gt; 38.3 ℃</td>
</tr>
<tr>
<td></td>
<td>- Heart Rate &gt; 90 / min</td>
<td>- Heart Rate &gt; 110 / min</td>
</tr>
<tr>
<td></td>
<td>- Respiratory Rate &gt; 20 / min</td>
<td>- Respiratory Rate &gt; 24 / min</td>
</tr>
<tr>
<td></td>
<td>- WBC &gt; 10,000 or &lt; 4000 or Normal WBC with &gt; 10% bands</td>
<td>- WBC &gt; 10,000 or &lt; 4000 or Normal WBC with &gt; 10% bands</td>
</tr>
<tr>
<td></td>
<td>- Other:</td>
<td>- Other:</td>
</tr>
<tr>
<td></td>
<td>- Altered mental status</td>
<td>- Altered mental status</td>
</tr>
<tr>
<td></td>
<td>- Hyperglycemia (&gt;140) in the absence of DM</td>
<td>- Hyperglycemia (&gt;140) in the absence of DM</td>
</tr>
</tbody>
</table>

### Inclusion Criteria

- Signs of SIRS + a source of infection

### Severe Sepsis

- Sepsis with Organ dysfunction

### Sepsis with Organ dysfunction

- Severe Hypoxemia, Metabolic Acidosis, Mental status changes, Oliguria, Increased Liver enzymes, coagulopathy

### Septic Shock

- Severe sepsis with Hypotension

<table>
<thead>
<tr>
<th>Signs of SIRS + a source of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of SIRS + a source of Infection</td>
</tr>
</tbody>
</table>

- Lactate > 4 mmol / L
**MATERNAL EARLY WARNING TRIGGERS**

- HR > 100 bpm
- MAP < 65 mmHg
- AMS
- TEMP > 38 ℃
- RR > 24/min
- SPO2 < 94%

**Sepsis Pathway**

- SIRS Present
- Severe Sepsis and Septic Shock

**Physician Assessment and Early Interventions**

- Severe sepsis and septic shock
- Physician assessment and ICU transfer

**Cardiopulmonary Pathway**

- Hypertension

**Hemorrhage Pathway**

- Hemorrhage

---

**Key Points**

- Obstetric patients commonly deteriorate progressively during an infectious process
- Identification of abnormal vitals and early interventions can decrease maternal morbidity and mortality
- MEWS may help in recognition of maternal physiologic changes during an acute infection and can trigger bedside evaluation by a healthcare team member

---

**Implementation of 1-3 Hour Resuscitation Bundle**

*At Each Shift Change Assessment must include Sepsis screening*

**Nurse Tech Role**

- Two or more SIRS criteria present
- Yes
- Get help and call RN

**RN Role**

- Possible source of infection present
- Yes
- Activate MD and infuse physician
- Start two large bore IV's
- Draw blood cultures, CBC, electrolytes, and serum lactate

**Physician Role**

- Start broad spectrum antibiotics
- Include a normal saline bolus if SBP < 60 mmHg or initial lactate is > 4 mmol/L
**Early Recognition**
- Implementation of Sepsis Screening Tool
- OB/RRT

**Early Interventions**
- One–Three Hour Bundle
- Six Hour Bundle

**Improved Outcomes**
- Improved morbidity and mortality

**Resuscitation Bundles**

**1-hour Bundle**
- Blood cultures obtained prior to antibiotic administration; additional cultures to determine potential site of infection
- Early and appropriate broad-spectrum antibiotic administration
  - within 3 hours for ED presentation.
  - within 1 hour for floor/ICU presentation.
- Measure Serum Lactate and repeat within 6 hours if initial level is > 2 mmol/L.
- In the event of hypotension and/or a lactate >4 mmol/L, deliver a minimum of 30 ml/kg of fluids in adults over 3 hours.

**Crystalloids Resuscitation**
- 30 ml/kg IBW and document in EHR
Antimicrobial initiation and Survival

Appropriate broad spectrum antibiotics
Route, dose, frequency and tissue penetration

Lactate and Sepsis

In patients with sepsis and septic shock, rising serum lactate of > 2 mmol/L have been linearly associated with risk of mortality during hospitalization, when compared to patients with serum lactate levels of < 2 mmol/L.

† Lactate levels is common in patients with severe sepsis or septic shock
† Lactate levels is a sign of tissue hypo-perfusion

Lactate clearance is associated with preserved organ function and improved survival – prolonged lactate clearance is associated with worsened multi-organ dysfunction

Resuscitation Bundles

6-hour Bundle

• Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65mmHg
  • Norepinephrine, Vasopressin and Epinephrine

• In the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥ 4 mmol/L, reassess volume status and tissue perfusion and document findings

• Re-measure lactate if initial lactate elevated
Leukopenia or Leukocytosis
Hyperglycemia in the absence of Diabetes

Common Lab Findings

Complete Blood count
With differential and platelets
Coagulation profile
PT, PTT, Fibrinogen
Electrolytes including BUN/Cr
Urinalysis and Cultures

Early DIC
- Thrombocytopenia, Decreased Fibrinogen levels, Increased PT and PTT
- Respiratory alkalosis with Increasing Metabolic Acidosis
- Increased Serum Lactate
- Low Arterial pH
- Increased base deficit

Laboratory Evaluation

Blood Cultures and culture all suspected sites
Chest X-Ray
CT Scan, Ultrasound and or MRI to localize Infections

Source Control

Common Sources of Infections in Sepsis

<table>
<thead>
<tr>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic Abortion</td>
<td>Endometritis</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>Wound Infection</td>
</tr>
</tbody>
</table>
Early Recognition
• Timely Intervention
• Implement 1-3 H and 6H care bundle

Prevent
• Prevent progression to organ failure
• Prevent Severe sepsis and septic shock

Evaluate
• Evaluate at regular interval
• Timely and safe disposition

Acute Organ Dysfunction

Respiratory
- PaO2/FiO2 < 200 if lung is the primary site of infection
- PaO2/FiO2 < 250 with other organ dysfunction

Liver and Metabolic
- Bilirubin > 2, or INR > 1.5
- Unexplained metabolic acidosis
- Lactate > 1.5 times upper normal

Skin
- Poor capillary refill
- Mottled skin

Neurologic
- Altered mental status, confusion, agitation, delirium

Cardiovascular
- SBP < 90 mmHg
- MAP < 65 mmHg (despite fluid resuscitation) and Need for Vasopressors
- UO < 0.5 ml/kg/Hr
- Serum creatinine > 2.0
- Platelet < 100,000/mm3
- Decline in platelet count of 50% over 3 days

Renal
- Respiratory
- Liver and Metabolic
- Cardiovascular

Tissue Perfusion Assessment

Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

Or Two of the following
- Measure CVP
- Measure ScvO2
- Bedside cardiovascular ultrasound evaluation
- Dynamic assessment of fluid responsiveness with positive leg raise or fluid challenge (SVV, PPV)
Management Goals for Severe Sepsis and Shock

- Red blood cell transfusion is recommended when the hemoglobin concentration decreases to <9.0 g/dL to target a hemoglobin concentration of 9.0 to 10.0 g/dL in adults.

Blood Products

- In the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease,

- Red blood cell transfusion is recommended when the hemoglobin concentration decreases to <9.0 g/dL to target a hemoglobin concentration of 9.0 to 10.0 g/dL in adults.

- FFP must not be used to expand volume or correct coagulation abnormalities in the absence of bleeding.

Mechanical Ventilation

- Lung Protective Mechanical Ventilation:
  - Target TV of 6 ml/kg of predicted body weight in patients with sepsis induced ARDS (Volutrauma)
  - Plateau pressure be measured and maintained < 30 cm of water (Barotrauma)
  - High PEEP to avoid alveolar collapse (Atelectrauma)
  - Maintain SPO2 > 96%
  - HOB elevation between 30 to 45 degrees to prevent development of VAP
Glucose Control and Nutrition therapy and Other Prophylaxis

- Protocolized approach to blood glucose management maintaining blood glucose < 180 mg/dL
- Treatment should avoid hyperglycemia (>180 mg/dL), hypoglycemia, and wide swings in glucose levels
- Administration of oral or enteral feedings, as tolerated, rather than complete fasting
- DVT and Peptic ulcer prophylaxis

Key Points

Early Recognition
- Implementation of Sepsis Screening tool

Early Interventions
- Three Hour

Improved Outcomes
- Improved morbidity and mortality
- Measure and Improve
- Continuous Quality Improvement (CQI)
Four Key Elements for Implementation of Early Sepsis Recognition

- Engaging hospital administration and clinical leadership
- Educate everyone who touches the patient (including patients and their families)
- Incorporate sepsis screening tool into EHR systems
- Auditing and collecting feedback using process and outcome data

Process for Improvement

- Develop and implement triggers for Sepsis Screens
- Early/ timely screening and identification of patients with sepsis/ severe sepsis
- Implement nurse/physician driven protocol (order-set)
- Physician notification and response
- Transition of care and handoffs
- Code Sepsis/ Rapid response team (RRT)
- Compliance data collection and implement rapid cycle change to improve

Implement and Improve

**LEADER**

L - Learn about sepsis and quality improvement by attending local and national sepsis meetings.
E - Establish a baseline in order to convince others that improvement is necessary
A - Ask for buy-in from institutional leadership
D - Develop an institution-specific SSC protocol comprising all bundle elements
E - Educate stakeholders
R - Remediate errors and anticipate obstacles along the way.
TAKEAWAY

A standardized approach should be formulated for pregnant women with suspected sepsis

Early Recognition, Fluid Therapy, and Timely appropriate antibiotics
Management protocol to include both maternal and fetal evaluation and treatment
Prevention strategies to prevent severe sepsis and septic shock

https://www.youtube.com/watch?v=bLGTgW2S64U

Thank You

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VACCINATION DURING PREGNANCY: A POWERFUL METHOD TO PREVENT INFECTION

Bernard Gonik, MD

Bernard Gonik, MD is currently a tenured professor and the Fann Srere Endowed Chair of Perinatal Medicine in the Division of Maternal-Fetal Medicine in the Department of Obstetrics and Gynecology at the Wayne State University School of Medicine. Dr. Gonik completed his undergraduate studies with honors at the University of Michigan and received his Doctor of Medicine degree at Michigan State University College of Human Medicine. He completed residency training in Obstetrics and Gynecology and fellowship training in Maternal-Fetal Medicine at the University of Texas Health Science Center in Houston. Dr. Gonik is a recognized academician and author of numerous scientific articles, book chapters and textbooks. His research interests include infectious diseases in obstetrics and gynecology, adult immunization, and shoulder dystocia dynamics. He is a fellow in the American College of Obstetricians and Gynecologists and a member of numerous professional societies including Infectious Diseases Society for Obstetrics and Gynecology, American Gynecological and Obstetrical Society, Society for Gynecologic Investigation, and Society for Maternal Fetal Medicine. Dr. Gonik recently returned from a one year sabbatical as a Jefferson Science Fellow with the National Academy of Sciences, Engineering and Medicine in Washington D.C. working in the Bureau of Maternal and Child Health at the United States Agency for International Development (USAID).
Vaccination During Pregnancy: A Powerful Method To Prevent Infection

Bernard Gonik, M.D.
Professor and Fann Srere Endowed Chair of Perinatal Medicine
Division of Maternal-Fetal Medicine
Wayne State University School of Medicine
Former Jefferson Science Fellow
National Academies of Science, Engineering and Medicine
Senior Science Advisor, Bureau for Global Health (MCHH/CHI), USAID

Global maternal and childhood mortality
All causes (2015-6)

- Maternal deaths 303,000
- Childhood deaths 5.6 Million (< 5 yrs age)
  - Neonatal deaths 2.6 Million
- Stillbirths 2.6 Million
- Overwhelming majority occur in low resource settings, particularly sub-Saharan Africa and South Asia
- A significant component are infection-mediated
Vaccine-preventable infectious diseases (VPD): Where are we now?

- Vaccines are a major contributor to the reduction in infection-related morbidity and mortality.
- Childhood vaccination universally adopted.
- Routine adult vaccination less well established.
- Immunization strategies during pregnancy thus far variably implemented.
- Data siloing limits the appreciation of vaccine benefits for both maternal and childhood health.
- Need to include morbidities as well as mortalities to better appreciate full extent of vaccine benefits.

Why discuss a maternal vaccine platform?

- Reduces maternal morbidity and mortality.
  - Via active immunization.
  - With few exceptions, vaccines safe, immunogenic and effective in pregnancy.
- Reduces fetal and neonatal morbidity and mortality.
  - Via passive transplacental antibody transfer.
  - Cocooning.
- Provides access to established VPD interventions with existing co-morbidities.
- Potential to reduce global health care inequities, antimicrobial resistance, and strengthen overall antenatal care.

What are potential candidates for the maternal vaccine platform?

- Globally established:
  - Tetanus.
- Developed countries:
  - Influenza, Pertussis.
- Globally underutilized, available and safe vaccines:
  - Pneumococcus, Meningococcus, Hepatitis A and B.
- Research in progress:
  - Primarily maternal focus:
    - HIV, Malaria, Emerging infections (e.g. Ebola).
  - Primarily newborn focus:
    - GBS, RSV, CMV, HBV, Emerging infections (e.g. Zika).
ACOG maternal immunization recommendations

Tetanus Toxoid component of WHD elimination program
Influenza vaccine encouraged by WHO but few countries have policies, little usage, limited efficacy data, and not financially supported by GAVI
No uptake for Pertussis vaccination
No data on vaccines for co-morbidities (HIV, SS, etc.)
Active ongoing research related to Influenza, Pertussis, RSV, GBS

Neonatal tetanus
Tetanus vaccination is not necessarily the best marker for a successful maternal vaccination program

  - ANC component of Tetanus elimination program
    - Documented 6 doses tetanus vaccine → no vaccine
    - Country elimination not achieved → 3 doses

- In 2015, approx 34,000 neonatal tetanus deaths (95% reduction)
- 15 countries still above target
- Suboptimal data collection on vaccination status, program compliance, tetanus cases
- Some improvements attributable to childhood vaccine series, clean births, “campaigns” outside of routine ANC

Vaccination during pregnancy may not be the primary mechanism for tetanus elimination

Influenza pandemic 1918 (“Spanish Flu”)

Globally:
- 500 M infected
- 50 M deaths

U.S.:
- 675K deaths

Influenza recognized as a serious infection disproportionately affecting pregnant women and their infants

- Worldwide 500,000 deaths annually
- Where data available, vaccine safe, immunogenic, and (mostly) efficacious for mom/baby
- In LMICs:
  - Platform exists (ANC) for vaccination
  - Despite being globally recommended, final WHO report on influenza epidemiology and vaccination during pregnancy (Fell DB, et al Vaccine 2017;35:5738-50) reported:
    - Low grade data on incidence, morbidities and mortalities in LMICs
    - Only 4 low resource RCT's (Bangladesh, SA, Mali, Nepal): Maternal vaccine efficacy 31-70%; infant efficacy 30-63%; mixed data on LBW, PTB
- In Developed Countries:
  - General consensus on flu vaccine recommendation
  - Broad range for utilization, including SES and other disparities

Effectiveness of maternal influenza immunization in mothers and infants. Zaman K et al. NEJM 2008;359:1555-64

- RCT in Bangladesh from 2004 to 2005
- Maternal inactivated Influenza vs Pneumococcal (control) vaccines (n=340)
- Followed weekly until 24 weeks after birth
- Subjects evaluated clinically for febrile respiratory illnesses/Infants tested for flu antigens

![Figure 3: Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.](image)
Influenza specific concerns with generalization

- Low resource settings (e.g., malnutrition, co-morbidities such as HIV, Malaria, etc.) may impair immune response to influenza vaccine and placental transfer
- Serotype selection heavily influenced by industrialized country epidemiology and may not match local viral serotypes
- Lack of seasonality in tropical climates does not allow for assessment of utility of current intervention strategies
- Population perceptions differ regarding disease burden, vaccine safety, and assumed efficacy
- Limited ANC, lack of CHW’s and supply chain logistics complicate vaccine delivery (and therefore likely vaccine uptake)


<table>
<thead>
<tr>
<th>Variable</th>
<th>Episodes</th>
<th>Influenza Vaccine</th>
<th>Clinical Effectiveness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal-months</td>
<td>876</td>
<td>881</td>
<td></td>
</tr>
<tr>
<td>Respiratory illness with fever</td>
<td>353</td>
<td>115</td>
<td>28.9 (8.9 to 48.7)</td>
</tr>
<tr>
<td>Temperature &gt;=38°C</td>
<td>77</td>
<td>96</td>
<td>28.1 (8.4 to 48.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>138</td>
<td>137</td>
<td>1.9 (0.0 to 26.0)</td>
</tr>
<tr>
<td>Clinical visit</td>
<td>92</td>
<td>34</td>
<td>63.9 (38.2 to 58.8)</td>
</tr>
<tr>
<td>Influenza test ordered</td>
<td>29</td>
<td>41</td>
<td>48.7 (21.4 to 66.7)</td>
</tr>
<tr>
<td>Influenza test positive</td>
<td>16</td>
<td>4</td>
<td>42.6 (9.0 to 85.4)</td>
</tr>
<tr>
<td>Mothers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal-months</td>
<td>1076</td>
<td>1089</td>
<td></td>
</tr>
<tr>
<td>Respiratory illness with fever</td>
<td>27</td>
<td>50</td>
<td>35.8 (2.7 to 57.2)</td>
</tr>
<tr>
<td>Temperature &gt;=38°C</td>
<td>33</td>
<td>19</td>
<td>45.1 (1.9 to 76.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68</td>
<td>49</td>
<td>19.3 (24.6 to 47.8)</td>
</tr>
<tr>
<td>Clinical visit</td>
<td>23</td>
<td>19</td>
<td>24.9 (4.9 to 60.8)</td>
</tr>
</tbody>
</table>
Resurgence of pertussis worldwide
- Waning immunity after childhood series
  - In U.S. 10-50,000 cases/year
- 2-3,000 cases infants < 3 months old
- Young children (< 1 yr old) disproportionately affected
  - 50% require hospitalization
    - 61% apnea; 23% pneumonia; 1% mortality
  - Too young for DTaP protection (starts @ 2 months)
- Typically acquired by close family member contact
- Adolescents and adults experience fewer complications, but can include
  - Prolonged cough, sleep disturbances, syncope, pneumonia, rib fractures

- KPNC 2010-15 Retrospective Study
- n = 148,981 infants
- Infant estimate vaccine efficacy:

<table>
<thead>
<tr>
<th></th>
<th>No Tdap (79,292)</th>
<th>Tdap (69,689)</th>
<th>Disease reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>15 cases</td>
<td>1 case</td>
<td>8.7</td>
</tr>
<tr>
<td>12 months</td>
<td>89 cases</td>
<td>22 cases</td>
<td>38.0</td>
</tr>
</tbody>
</table>

- Review of 46 RCTs, prospective and retrospective cohort, case-control, and observational studies
- 345,000 participants
- Pertussis vaccines immunogenic in pregnancy
- Efficient transplacental passage in 2nd and 3rd trimesters
- High VE (approximately 90%) early in life; extended benefit beyond 6 months in some studies
- Overall reassuring evidence for safety in mothers and infants
  - Small increase in chorioamnionitis and postpartum hemorrhage (biologic plausibility?)
  - Infant immunologic blunting; no clinical correlates and correction with booster

Newborn GBS sepsis

- Globally 21.7 million pregnant women colonized (approx 1 in 5)
- Maternal impact
  - 33,000 cases maternal invasive disease
- Fetal/infant impact
  - 57,000 stillbirths
  - 320,000 infants with sepsis and meningitis
  - 50,000 neonatal deaths
- Intrapartum antibiotic prophylaxis effective, but limited impact on maternal disease, stillbirths, and late onset neonatal disease
- Insufficient levels of coverage based on inequitable factors
- No impact of strengthening ANC; may be compromised by missing ANC visits
- Maternal vaccination (80% efficacy, 90% coverage) could prevent 229,000 maternal cases, 41,000 stillbirths, and 67,000 infant deaths

Making the case for a maternal Group B Streptococcus (GBS) vaccine

- Seale AC, et al. CID 2017;65:S200-19
GBS vaccines in development

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Construct</th>
<th>Development phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Multivalent CPS conjugate</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Novartis</td>
<td>Trivalent CPS conjugate</td>
<td>Phase 2</td>
</tr>
<tr>
<td>GSK</td>
<td>Pentavalent CPS-CRM</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Bionovax</td>
<td>PIlus proteins</td>
<td>Discovery</td>
</tr>
<tr>
<td>Minervax</td>
<td>N-domain Rib surface proteins</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

Slow progress for the maternal GBS vaccine

- Low maternal IgG sero-specific levels linked to newborn GBS susceptibility (biologic plausibility)
- Robust maternal immune responses to antepartum vaccination
- Good 3rd trimester antibody transfer
- Excellent safety profile
- No established serology correlates for protection
- Regional differences in serotypes (need for multivalent vaccine of common antigen targets)
- Limited data on region-specific GBS epidemiology
- Lack of industry standards for assay validation
- Very limited human data, mostly animal models (good protection)

Maternal GBS vaccine concerns

- Lack of country specific serotype data (Madrid L et al. 2017;65:S160-72)
- Lack of accurate prevalence data (Dagniew AF et al. CID 2012;55:91-102)
- Lack of country specific vaccine efficacy data (and ethical concerns regarding studies where antibiotic prophylaxis currently utilized)
- Anticipated vaccine cost/effectiveness (Russell LB et al. Vaccine 2017;36:6905-14)
- Unclear approach to vaccination (i.e. treat all or only colonized); might require more complex ANC initiatives
Respiratory syncytial virus pneumonia

Making the case of a maternal RSV vaccine

- Common, highly contagious viral pathogen resulting in yearly epidemic outbreaks
- Leading viral cause of acute LRTI (bronchiolitis, pneumonia) among infants and young children
- 33.8 million episodes of RSV associated acute LRTI each year worldwide
- RSV leads to approx 5-15% of all childhood CAP cases
- Globally
  - 2.8 to 4.3 million RSV hospitalizations (90% in developing countries)
  - 53,000 to 199,000 RSV related infant deaths/yr (99% in developing countries)
- Association with long term respiratory compromise (wheezing, asthma)

Geoghegan S, et al. AJRCCM 2017
Vaccination of pregnant women with RSV vaccine and protection of their infants. Madhi SA, et al. NEJM (accepted)

- First ever large scale efficacy trial of an investigational vaccine in pregnancy
- International RCT (n=4,636); funded through BMGF (70 M); timed for RSV seasons
- 28-36 wks; nanoparticle RSV-F protein vaccine

Safety
- Local rxns: 57% vs 41% (p < 0.001)
- Systemic rxns: 1.2% vs 1.6%
- Serious AE: 46.4% vs 44.3%
- Immunogenicity
  - 12 G1 bar rise
  - Cord/Infant antibody transfer 1.94

Efficacy (through 90 days post delivery)
- RSV/LRT/All cause pneumonia 4.8% vs 4.9% (180 days)
- Symptomatic PP maternal RSV disease 4.9% vs 4.8% (180 days)
- RSV/LRT/Hospitalization 4.4%
- RSV/LRT/severe hypoxemia 8.8%
- All cause pneumonia 5%
- Symptomatic PP maternal RSV disease 4.8% vs 4.9% (180 days)

Graphic modeling of maternal vaccine effect - RSV
Other potential vaccine candidates studied

- Cochrane Reviews on maternal vaccination strategies for reductions in neonatal morbidities and mortalities with insufficient evidence:
  - Pneumococcus
  - Hepatitis B
  - Haemophilus influenza B

WHO recommended elements to be addressed when considering maternal vaccine introduction

Predictors of maternal vaccination

- Provider recommendation
- Knowledge, attitudes, beliefs
- Cues to action
- Geography, race, ethnicities
- Logistics
  - Standing orders
  - Personnel
  - Access to vaccines
  - Cost
  - Supply chain

Myers KL. Vaccine 34:3942-9;2016
Patelwadi M and Gonik B. J Women’s Health Safety 4(1):90-8;2019
Thank you for your participation!

Please complete the survey, as your input is very important to the Department of Obstetrics and Gynecology when planning future educational events: https://www.surveymonkey.com/r/TYKG875

Syllabus is available online at: http://obgyn.med.wayne.edu/wayne-day

Additional questions – contact: Alaina Bruce-Jackson at: 313-993-4027, or abruce@med.wayne.edu

Happy Holidays....