Updates on COVID-19 in Children and People of Reproductive Age

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Overview of Presentation

• COVID-19 Effects on Female and Male Reproductive Systems
• COVID-19 and Vaccination in Pregnancy and Lactation
• Multi-system Inflammatory Syndrome in Children (MIS-C)
  ▪ Progress in PreVAIL klds initiative
• Future Challenges
COVID-19 Effects on Female and Male Reproductive Systems
COVID-19 Vaccinations and Menstruation

• Anecdotal reports of changes to menstrual cycles amplified by major media outlets
  ▪ Reported changes to cycle timing (longer or shorter cycles, skipped periods, breakthrough bleeding between cycles), flow (heavier or lighter than normal), and comorbidities such as increased pain during cycles

• Data on menstrual changes were not collected during vaccine safety trials

• NICHD surveyed potentially applicable parent studies, wrote and published a NOSI (NOT-HD-21-035)

• Awarded $1.67M to five institutions in August 2021
COVID-19 Vaccination and Menstruation Awards

- Prospective pre-conception study of >15,000 geographically and racially/ethnically diverse women. Extensive control of confounders like stress and information bias. (Boston University, PI: Lauren A. Wise, ScD)

- Focuses on adolescents who are being followed in a gynecologic pain study; will collect saliva for hormone and immune markers. (Harvard Medical School, PI: Laura Allen Payne, PhD)

- Supplements existing cohort using menstrual diary tracking with additional recruitment; examining menstrual effluent. (Johns Hopkins University, PI: Mostafa Borahay, PhD)

- Uses existing cohorts (>65,000 female participants) with menstrual tracking for years; one oversamples for people with endometriosis and regularly collects blood samples. (Michigan State University, PI: Stacey Ann Missmer, ScD)

- Uses preexisting US-based datasets from FDA-approved fertility awareness applications (pandemic data from >2 million US women). (Oregon Health and Science University, PI: Alison B. Edelman, MD)
COVID-19 Vaccination and Menstruation – Early Results

• Analyzed de-identified data from nearly 4,000 women via a fertility tracking app
• One dose of a COVID-19 vaccine during a single menstrual cycle increased cycle length by nearly one day compared to unvaccinated women
  ▪ Two vaccine doses in same menstrual cycle increased cycle length by ~ 2 days
  ▪ Increased cycle length not associated with change in the number of days of menses
  ▪ Changes were temporary; cycle length returned to normal in subsequent cycles
  ▪ International Federation of Gynecology and Obstetrics classifies a variation in cycle length as normal if the change is less than eight days
• Additional research may determine if COVID-19 vaccination influences associated menstrual symptoms (e.g., pain, mood changes) and characteristics of bleeding (e.g., heaviness of flow)

COVID-19 Effects on the Male Reproductive System

• NICHD has a research portfolio in male reproductive health

• COVID-19 can temporarily reduce male fertility
  ▪ 18% lower chance of conception if male partner has SARS-CoV-2 infection within 60 days before menstrual cycle
  ▪ Testing positive for SARS-CoV-2 did not appear to affect overall conception rates

• COVID-19 causes higher rates of erectile dysfunction
  ▪ Coronavirus can infect tissue within the male genital tract, where it may linger long after the initial infection
  ▪ Not enough evidence yet for a causal link

A Prospective Cohort Study of COVID-19 Vaccination, SARS-CoV-2 Infection, and Fertility


http://doi.org/10.1093/aje/kwac011
COVID-19 and Vaccination in Pregnant and Lactating People
Maternal, Placental and Fetal Immune Response to the COVID-19 Vaccines

• Increased SARS-CoV-2 antibody levels in pregnant people post-vaccination vs. natural infection (Gray KJ et al. AJOG, 2021)

• Maternal immune responses were superior if vaccinated during the third or first trimester (Atyeo et al., Medrxiv, 2021)
  - Maternal cord transfer was highest in 1st trimester vaccination
  - Potential maternal and fetal benefits with earlier vaccination in pregnancy

• Vaccine-induced antibodies are present in breast milk samples (Gray KJ et al. AJOG, 2021)

• Best protection for an infant is to vaccinate the mother during the third trimester and have the mother breast feed
Vaccinating Pregnant People Protects Infants Against COVID-19

• CDC case-control study examined data including 379 COVID-positive infants at 20 pediatric hospitals in 17 states from July 1, 2021–January 17, 2022

• Effectiveness of maternal mRNA vaccination during pregnancy against COVID-19 hospitalization in infants aged <6 months was 61%

• First epidemiologic evidence for the protective benefits of maternal immunization during pregnancy against COVID-19 in infants


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Multi-system Inflammatory Syndrome in Children (MIS-C)
Predicting Viral-Associated Inflammatory disease severity in children with Laboratory diagnostics and artificial Intelligence (PreVAIL klds)

*Note: MIS-C is a form of post acute sequelae of COVID-19 also known as Long COVID

Goals: Develop translational tools to understand the spectrum of pediatric SARS-CoV-2 illness, rapidly diagnose and characterize MIS-C associated with SARS-CoV-2, and predict the longitudinal risk of disease severity after exposure to and/or infection by SARS-CoV-2

Includes:
- Genetics, Omics, and other Biomarkers
- Viral Dynamics and Immune Profiling Studies
- Digital Health Platforms Leveraged for Children
- Artificial Intelligence

- Funded through RADx®-Radical initiative
More than Funding: Small Business Education and Entrepreneurial Development (NIH SEED)

NIH Office of the Director / NIH Office of Extramural Research

• Supports the NIH innovator community (funding and resources) to validate and advance discoveries to products that improve patient care and health

• Allows investigators to:
  • Develop relationships with strategic partners and build opportunities for NIH innovators to further their product development efforts.
  • Meet early with the FDA and apply for EUAs
  • Move quickly to translation

smallbusinessinnovationinnovatoracademicsupport.seed.nih.gov
Project Aim: To use RNA, protein, antibody, or clinical parameters to predict progression to severe COVID and MIS-C

- Enrolled ~3200 participants in a US cohort with a collaboration in the UK
- Pre-EUA package for the diagnostic algorithm, KIDMATCH, is currently being reviewed by FDA. Diagnostic algorithm demonstrated to distinguish MIS-C, Kawasaki, and other febrile illnesses with >95% accuracy
- Team plans to expand the prediction algorithm work by validating by qPCR a previously identified diagnostic signature for MIS-C
- Analyzing proteins that can identify MIS-C by lateral flow using technologies like Somamers and ELISA
AI Signature Shows Shared Immune Response Between Kawasaki Disease and MIS-C

- Study based on publicly available KD datasets, newly recruited cohorts of KD and MIS-C, data on children with COVID-19, and data on a set of febrile control children
- Used AI to assess the host immune response
- Similar profiles of host immune response in COVID-19, MIS-C and KD: upregulation of IL15/IL15RA pathways
- A genetic signature for KD that previously distinguished KD from other febrile diseases was similar in MIS-C
- KD and MIS-C share molecular markers; thus they may share proximal pathways of immunopathogenesis, but immune features may diverge later in disease process
  - Degree of host response in MIS-C higher than in KD
    - Pro-inflammatory pathways MIP1a, TNFa and IL1 significantly induced in MIS-C compared to KD
- Authors therefore recommend anakinra + infliximab to treat MIS-C

Project Aims: To characterize a full range of markers across the pediatric COVID patient population to train machine learning algorithms/ensembles to identify progressive disease cases at initial presentation

- Enrolled about 400 participants prospectively and about 50,000 participants retrospectively in or near Texas
- Preparing a Pre-EUA package based on an inflammatory cytokine/chemokine panel (*image at right*)
- Plans to expand this prediction algorithm to standard lab records, EMR free text, and chest radiographic images
- Highlighted impact of socio-economic disparities and race association with disease severity. Non-Hispanic Black children and children in high deprivation index areas are significantly more likely to require intubation and/or vasoactive support (adjusted for gender and BMI)
Future Challenges
- 9.9 M children ages 5-11 (35%) have received at least one dose of COVID-19 vaccine
- 8.1 M children ages 5-11 (28%) are fully vaccinated
- 17.2 M children and adolescents ages 12-17 (68%) have received at least one dose of COVID-19 vaccine
- 14.7 M children and adolescents ages 12-17 (58%) are fully vaccinated
- 25K children and adolescents ages 12-17 received their first dose this week
Potential Impact of Maternal SARS-CoV-2 Infection on Fetal Neurodevelopment

- Past pandemics have provided a window into potential neurodevelopmental consequences in subsequent generations
- Maternal and placental immune activation can affect the developing brain
- Some reports show potential connection between prenatal SARS-CoV-2 exposure and neurodevelopmental disorders in offspring; too early for definitive diagnosis for many conditions
- Future variants with enhanced immune escape or transmissibility could impact risk for transplacental infection (currently rare)
- Future research needs
  - Cellular models of fetal brain development to better understand potential short- and long-term impacts of maternal SARS-CoV-2 infection on offspring
  - To understand not only direct/immediate effects, but also persistent effects on cells
  - More data on all trimesters for holistic risk assessment

Future Pandemic Preparedness: Include Pregnant and Lactating People in Research

• Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
  ▪ Representation across all sectors
  ▪ Issued recommendations in 2018 and an implementation plan in 2020
    • https://www.nichd.nih.gov/About/Advisory/PRGLAC

• Change the culture to protect pregnant people through research instead of from research

• Need to plan for the inclusion of pregnant and lactating people for evaluation of treatments and vaccines in future pandemics
Thank You!

Questions?